American Heart Journal

An international publication for the study of the circulation

GEORGE E. BURCH M D
Editor

HARRY L COLCOLOUGH
NICHOLAS P DePASQUALE, M D
JOHN H PHILLIPS M.D
Assistant editors

1430 Tulane Avenue New Orleans La 70112
The C V Mosby Company 3207 Washington Blvd., St. Louis Mo 63103

VOLUME 73

JANUARY JUNE, 1967

VOLUME 73

Printed in the United States of America

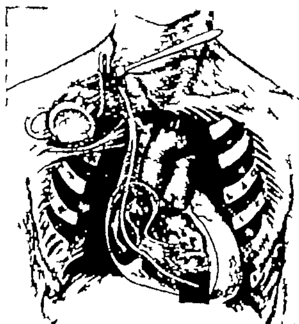
American Heart Journal
JANUARY 196

Contents

Editorial

continued on page 3

Implant pacing with endocardiac electrode



Endocardiac electrode in combination with a subcutaneously implanted pulse generator permits long term pacemaking without the need for thoracotomy

Long-term pacemaking ca be achieved by means of an impla ted system using a permanent endocardiac electrode attached to a pulse generator placed into the subcutaneous tissue of the a terior chestwall.

The indwelli g catheter is placed into the right ventricle via the external jugular vein. The pulse generator is nserted into a pocket formed either beneath the pectoralis majo or n the subcutaneous layer

The system can be implanted under local anesthesia, eliminat g the need for thoracotomy *in the high risk patient.*

The Model 5870-C Pulse Generator is sim lar to the standa d 5870 Chardack-Greatbatch Implantable Pacemaker except for m nor design changes which make t particularly su table for use with the endocardiac electrode.

Rate and amplitude (40 to 120 pulses per minute, 0 to 6 m ll amperes) are adjustable before o after implantation by puncture with a needle of triangular cross section.

The Model 5816 Chardack Endocardiac Electrode consists of two hel cal stainless steel co l springs traveling   separate lum na of s licone tubing. The two coils are welded to a platinum ring and tip wh ch form the electrode terminals in contact with the right ventricular wall

Two stylets provide the st ffness curvature of the tip and axial rotation requ red for nsertion. *When the electrode is in place the stylets are removed, leaving a extremely soft pliable* structure wh ch complies with card ac motion.

This electrode conf guration is bipolar but may be transformed into a monopolar arrangement if desired.



Medtronic, Inc

[illegible] OLD HIGHWA[illegible] [illegible] MINNEAPOLIS [illegible]

[illegible]

Contents *continued*

Vol. 73, No. 1, January 1967 American Heart Journal is published monthly by The C. V Mosby Company 3207 Washington Boulevard, St. Louis, Mo., 63103 Second class postage paid at St. Louis, Mo., and at additional offices. Subscription rates: United States and Its Possessions $1 00; Canada, Latin America and Spain $17 00, Other Countries $17.50 Students, interns, and resident physicians: United States and Its Possessions $8 40; Canada, Latin America and Spain $9 40; Other Countries $9 90, Single copies $1.50 postpaid. Printed in the U S. A.
The C. V Mosby Company

American Heart Journal

FEBRUARY 1967

Contents

continued on




KENDALL

Contents *continued*

continued

Contents *continued*

Fundamentals of clinical cardiology

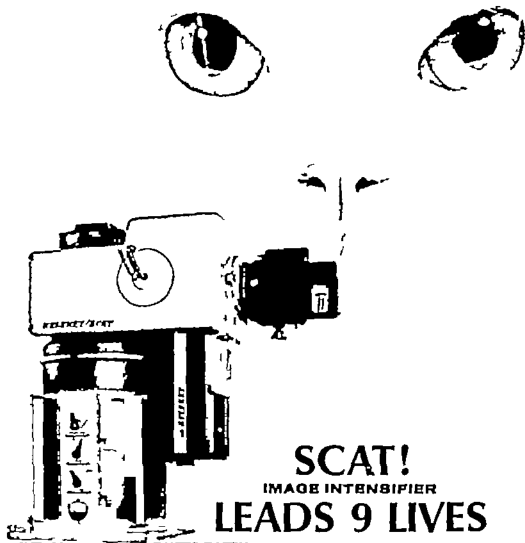
Appraisal and reappraisal of cardiac therapy

Annotations

Book review

Announcements

Vol. 73, No. 2, February, 1967. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo., 63103. Second class postage paid at St. Louis, Mo., and at additional offices. Subscription rates: United States and Its Possessions $[illegible], Canada, Latin America and Spain $17.00, Other Countries $17.50. Students, interns, and residents [illegible] United States and Its Possessions $[illegible], Canada, Latin America, and Spain $[illegible], Other Countries $[illegible]. Single copies $[illegible] postpaid. Printed in the U. S. A. Copyright © 1967 by The C. V. Mosby Company.


SCAT!
IMAGE INTENSIFIER
LEADS 9 LIVES

American Heart Journal

MARCH 1967

Contents

continued on

a built-in safety factor in digitalis therapy for geriatric patients



Elderly patients are more prone to overdigitalization and toxicity. The zone between digitalization and digitoxicity becomes narrower with advancing age.

Smooth maintenance is possible with the use of *powdered leaf digitalis*. Overdosage or intolerance with *powdered leaf digitalis* is usually signalled by anorexia, nausea and vomiting, diarrhea or visual disturbances — a "built-in safety factor" to help avoid serious cardiac arrhythmias. These traditional warnings are often absent when certain purified crystalline preparations are utilized.

REFERENCES: 1) Herrmann, G.R.: Geriatrics 21:109, 1966 2) Reed, R.R. and Andersen, M.W.: JH Lancet 86:47, 1966 3) Dall, J.L.C.: Lancet 1:194, 1965 4) Herrmann, G.R.: J.A.M.A. 191:776, 1965 5) Dubnow, M.H. and Burchell, H.B.: Ann. Int. Med. 62:956, 1965

DOSAGE: Dosage should be carefully regulated to individual requirements of each patient. Average Oral Dose: rapid digitalization — 1.5 Gm. (22½ gr.) — 0.6 Gm. initially, followed by 0.2 Gm. every six hours until digitalization accomplished; slow digitalization — 0.2 Gm. daily for 3 to 7 days; maintenance — 0.1 Gm. (1½ gr.) daily.

CAUTION: Digitalis therapy should be withheld when signs of intoxication appear. Toxicity is more frequently encountered in patients with hypokalemia, hypothyroidism, advanced hepatic or renal disease, and in aged or debilitated patients. Potassium depletion, usually caused by diuretic agents, or electrolyte manipulations sensitize the heart to digitalis.

AVAILABILITY: 0.1 Gm. (1½ gr.), 60 mg. (1 gr.), 60 mg. ([illegible] gr.) and 30 mg. (½ gr.) pills in bottles of 100.

PIL-DIGIS®

brand of
powdered leaf digitalis

also known as PIL. DIGITALIS (Davies, Rose®)

DAVIES ROSE-HOYT

Pharmaceutical Division
The Kendall Company
Needham, Mass. 02194



Contents *continued*

continued on page 8

Contents *continued*

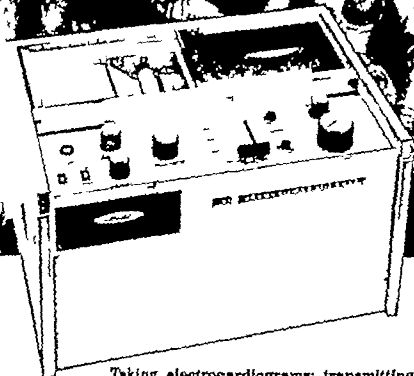
Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews

Announcements

Vol. [illegible], No. 3, March, 1967. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo., 63103. Second class postage paid at St. Louis, Mo. Subscription rates: United States and Its Possessions $ 6.00; Canada, Latin America, and Spain $1 .00; Other Countries $17.50. Students, interns, and resident physicians: United States and Its Possessions $[illegible]; Canada, Latin America, and Spain $9.00; Other Countries $9.50. Single copies $2.00 postpaid. Printed in the U. S. A.



Taking electrocardiograms; transmitting ECGs via telephone recording phonocardiograms and photomotograms (Achilles tendon reflex) with auxiliary equipment, a teaching aid in medical schools. The Burdick EK 4 becomes a many dimensioned diagnostic facility to reduce the need for patient referral thus strengthening your physician-patient relationship Burdick's dual-speed EK 4 offers the latest innovations in ECG equipment—yet stresses dependability and diagnostic accuracy as always Serviced through technically-knowledgeable dealers who know the equipment and understand the needs of the doctor—little wonder the Burdick electrocardiograph is the choice of so many medical schools and teaching institutions.

EK4 Electrocardiograph



Burdick EK 4 Console Unit

THE BURDICK CORPORATION
MILTON WISCONSIN 53563

American Heart Journal

APRIL 1967

Contents

Editorial

Clinical communications

continued on page 3

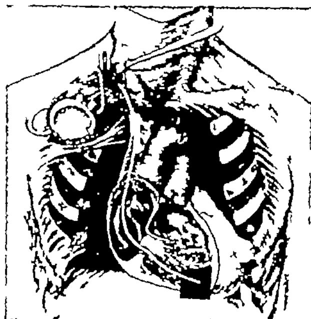
Contents *continued*

Experimental and laboratory reports

Case reports

Clinical pathologic conference

Implant pacing with endocardiac electrode



Endocardiac electrode in combination with a subcutaneously implanted pulse generator permits long term pacemaking without the need for thoracotomy

Long term pacemaking can be achieved by means of an implanted system using a permanent endocardiac electrode attached to a pulse generator placed into the subcutaneous tissue of the anterior chestwall

The indwelling catheter is placed into the right ventricle via the external jugular vein. The pulse generator is inserted into a pocket formed either beneath the pectoralis major or in the subcutaneous layer

The system can be implanted under local anesthesia, eliminating the need for thoracotomy in the high risk patient.

The Model 5870-C Pulse Generator is similar to the standard 5870 Chardack-Greatbatch Implantable Pacemaker except for minor design changes which make it particularly suitable for use with the endocardiac electrode.

Rate and amplitude (40 to 120 pulses per minute 0 to 6 milliamperes) are adjustable before or after implantation by puncture with a needle of triangular cross section.

The Model 5816 Chardack Endocardiac Electrode consists of two helical stainless steel coil springs traveling in separate lumina of silicone tubing. The two coils are welded to a platinum ring and tip which form the electrode terminals in contact with the right ventricular wall.

Two stylets provide the stiffness, curvature of the tip and axial rotation required for insertion. When the electrode is in place the stylets are removed leaving an extremely soft pliable structure which complies with cardiac motion.

This electrode configuration is bipolar but may be transformed into a monopolar arrangement if desired.


Medtronic, Inc

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Letter to the Editor

Book reviews

Announcements

Vol. 73, No. 4, April, 1967 American Heart Journal is published monthly by The C. V. Mosby Company 3207 Washington Boulevard, St. Louis, Mo 63103 Second class postage paid at St. Louis, Mo Subscription rates: United States and Its Possessions $16.00; Canada, Latin America and Spain $17.00 Other Countries $17.50 Students, interns, and resident physicians United States and Its Possessions $8.40; Canada, Latin America, and Spain [illegible] Other Countries $9.90. Single copies $1.50 postpaid. Printed in the U. S. A.

American Heart Journal

MAY 1967

Contents

continued on page 3

Contents *continued*

continued on page 5

Contents *continued*

Review

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews

Announcement

Vol. 73, No. 5, May, 1967. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo., 63103. Second class postage paid at St. Louis, Mo. Subscription rates: United States and Its Possessions $1... 00; Canada, Latin America and Spain $1... 00; Other Countries $17.50. Students, interns, and resident physicians: United States and Its Possessions $8.50; Canada, Latin America, and Spain $9.40; Other Countries $9.90. Single copies $1.50 postpaid. Printed in the U. S. A.

American Heart Journal

JUNE 196

Contents

continued

Contents *continued*

continued on page 4

Contents *continued*

Announcements

Index

Vol. 73, No. 6, June, 1967 American Heart Journal is published monthly by The C. V Mosby Company 3207 Washington Boulevard, St. Louis, M 63 03 Second class postage paid at St. Louis, M Subscription rates: United States and Its Possessions $16 00 Canada, Latin America and Spain $17 00 Other Countries $17 50 Students, interns, and resident physicians: United States and Its Possessions $8 40, Canada, Latin America, and Spain $9 40 Other Countries $9 90. Single copies $1 50 postpaid Printed in the U S. A.

American Heart Journal

January 1967 Volume 73 Number 1

Editorial

Recurrent coarctation of the aorta

Clifford G Parsons M.D F.R C P
Birmingham England

Recurrence of coarctation after an apparently successful operation is an unusual but well-authenticated complication Cerilli and Laurdsen collected 6 examples in a series of 142 surgically treated cases, and more recently there has been a report of 8 children with recurrent coarctation[2]

In babies, the recurrence of narrowing may happen remarkably quickly Two almost identical examples of this were reported by d Abreu and Parsons[3] in 1956 and by Mulder and Linde[4] in 1959 In each case end to-end anastomosis was effected after resection of a clearly defined narrow aortic segment close to the ductus arteriosus. Femoral arterial pulsation was good at first, but within a few weeks the arterial pulse in the legs disappeared and a fresh tightly constricted coarctation was demonstrated by angiography In one of the cases a second operation was performed 7 weeks after the first. The resected specimen had marked proliferative changes in the aortic wall and the lumen measured only 1 0 mm. in diameter The appearance was identical with that of the previously resected segment. There was no evidence of the thrombus formation and Mulder and Linde[4] suggest that since they made their incision into the aorta very close to the ductus, they might have left tissue with an inherent propensity for constriction.

Not everyone accepts the skodaic theory as a satisfactory explanation of coarctation it certainly could not account for recurrence of coarctation in older children or adults. Edwards and his colleagues[5] regard coarctation as a progressive condition. They described intimal thickening and a sphincter like projection of the aortic media which narrows the lumen in an eccentric manner Cerilli and Laurdsen operated on a number of patients with recurrent coarctation and observed thickening of the suture line with a ridge of intima which greatly reduced the diameter of the lumen. This was observed in a 24-year-old man $2\frac{1}{2}$ years after what was regarded as being a successful operation. They thought that the explanation might be that too large a bite of aorta was taken when the anastomosis was done. A second example was in a 19-year-old man in whom a Teflon graft had been inserted In this case, the thick ridge was at the suture line and was ascribed to damage done when the graft was inserted

However we have watched coarctation developing *ab initio* A 7 year-old boy was being examined by angiocardiography

Received for publication June 28, 1966.

*The Children Hospital, Ladywood Rd., Birmingham 6, England.

as a preliminary to an operation on congenital pulmonic stenosis. Quite unexpectedly he was found to have slight narrowing of his aorta in addition to the abnormal pulmonary valve. He had no objective evidence of coarctation. But 2 years later his femoral pulses could no longer be felt and the blood pressure in his legs was unobtainable. Aortography showed that the affected segment of aorta was very much narrower and when examined after resection showed a medial spur similar to that described by Edwards and associates. Intimal changes were slight and there was no evidence of previous thrombosis. A long Teflon graft was inserted and the femoral pulses returned to normal but a week later they could no longer be felt and a month afterward angiocardiography showed a new area of narrowing at the lower end of the graft well below the previous constriction.

When one is trying to explain this progressive stenosis, it is natural to think in terms of clotting at the suture line. Certainly clotting can lead to progressive narrowing of the aortic lumen but there was no definite evidence that it was responsible in any of our cases and it seems to be most unlikely that thrombosis played any part in the obstruction which developed before operation.

Rodbard demonstrated that if the velocity of fluid flowing through a slightly narrow section of tube is increased beyond a critical level the outward distending pressure of the fluid diminishes and cushions form which lead to increasing constriction of the lumen. If operation or a developmental anomaly were to disturb the pattern of blood flow in the aorta, changes in velocity might initiate narrowing and lead on to coarctation.

Rodbard's experiments provide a possible explanation of recurrent coarctation. They also explain why patients who are left with a relatively narrow anastomosis do not necessarily deteriorate; indeed they may improve.[2] Presumably the velocity of the blood in these patients never reaches the critical level necessary to initiate the process of constriction. And this in turn no doubt depends on the gradient across the anastomosis.

A postoperative review of 118 patients with measurements of aortic pressure and aortography led Frederiksen and Jagt[9] to conclude that when the area at the narrow point is 40 per cent or more of the area of the aorta at the level of the diaphragm the systolic gradient across the anastomosis will be less than 10 mm. Hg.

Rathi and Keith reviewed the cases of 150 patients after operation in infancy or childhood. The blood pressure in the legs did not always rise above that in the arms but they found no evidence of recurrent coarctation or of failure of the anastomotic ring to grow with the child.

There are several reasons for thinking that the rate of growth of the anastomotic junction is not an important factor. (1) Although it is true that most examples of restenosis occur as a sequel to operation on a growing child and especially an infant, the condition is seen also after operations in adults. (2) Although it may take years for the femoral pulse to fade and the blood pressure in the legs to fall, the whole process is sometimes condensed into a period of a few days. (3) The eventual stenosis may be much narrower than the lumen left by the surgeon at the end of the operation, which suggests that there must be an active process of constriction, not just a passive failure of growth.

When recurrence of coarctation has been clearly demonstrated, the decision has to be made whether to perform a second operation. Because some cases of restenosis seem to improve spontaneously as the child grows, it is clearly essential to be sure that operation is required. This involves measuring the gradient across the narrow segment by catheterization and outlining the aortic lumen by aortography.

If operation is undertaken the hazards are considerable. The aortic wall tends to be thin and brittle and may blow up into an aneurysm both above and below the anastomotic ring. Paraplegia has been noted as a result of operation. The surgical mortality is about three times that of the initial operation.[3]

With regard to the initial operation, the risks are smallest just before puberty and much greater in infancy.[13,14] Most pediatric cardiologists accept the view that an infant

with coarctation and heart failure should be treated vigorously with digitalis and diuretics, and only when the response to medical treatment is inadequate should a baby be referred for surgery.[1, 17] Many of these babies will have other cardiac malformations, and the hazards of operation are considerable.[18,19] There is little evidence that the anastomotic junction fails to grow but there is no doubt that occasionally after a satisfactory anastomosis, progressive narrowing of the aortic lumen may lead on to severe stenosis. The reason for this is still a mystery, and further work on the subject is desirable.

REFERENCES

1. Cerilli, J. L., and Lauridsen, P.: Reoperation for coarctation of the aorta, Acta Chir. Scandinav. 129:391, 1965.
2. Parsons, C. G., and Astley, R.: Recurrence of aortic coarctation after operation in childhood, Brit. M. J. 1:573, 1966.
3. D'Abreu, A. L., and Parsons, C. G.: Surgical treatment of children with coarctation of the aorta, Brit. M. J. 2:790, 1956.
4. Mulder, D. G., and Linde, L. M.: Recurrent coarctation of the aorta in infancy, Am. Surg. 25:908, 1959.
5. Edwards, J. E., Christensen, N. A., Clagett, O. T., and McDonald, J. R.: Pathologic considerations in coarctation of aorta, Proc. Staff Meet. Mayo Clin. 23:324, 1948.
6. Ullal, R., and Braimbridge, M. V.: Acquired coarctation of the thoracic aorta due to calcified thrombus, Ann. Surg. 162:246, 1965.
7. Rodbard, S.: Vascular modifications induced by flow, Am. Heart J. 51:926, 1956.
8. Rodbard, S.: Physical factors in the progression of stenotic vascular lesions, Circulation 17:410, 1958.
9. Frederiksen, T., and Jart, T.: Coarctation of the aorta. Criteria for assessing operative result on the basis of thoracic aortography, Acta Chir. Scandinav. 130:458, 1965.
10. Rathi, L., and Keith, J. D.: Postoperative blood pressure in coarctation of the aorta, Brit. Heart J. 26:671, 1964.
11. Frederiksen, T., and Poulsen, T.: Paralysis of the lower limbs following reoperation for coarctation of the aorta. Report of one case, Acta Chir. Scandinav. 127:252, 1964.
12. Schuster, S. R., and Gross, R. E.: Surgery for coarctation of the aorta. A review of 500 cases, J. Thoracic & Cardiovas. Surg. 43:54, 1962.
13. Sellors, T. H., and Hobsley, M.: Coarctation of the aorta. Effect of operation on blood pressure, Lancet 1:1387, 1963.
14. Nadas, A. S.: Pediatric cardiology, ed. 2, Philadelphia, 1963, W. B. Saunders Company.
15. Waldhausen, J. A., King, H., Nahrwold, D. L., Lurie, P. R., and Schumaker, H. B., Jr.: Management of coarctation in infancy, J.A.M.A. 187:270, 1964.
16. Lang, H. T., Jr., and Nadas, A. S.: Coarctation of aorta with congestive heart failure in infancy—Medical treatment, Pediatrics 17:45, 1956.
17. Freundlich, E., Engle, M. A., and Goldberg, H. P.: Coarctation of aorta in infancy. Analysis of 10-year experience with medical management, Pediatrics 27:427, 1961.
18. Bull, C., Hoekema, T., Duckworth, J., W., and Mustard, W. T.: An experimental study of the growth of arterial anastomoses, Canad. J. Surg. 6:363, 1963.
19. Mahn, J. R., Blumenthal, S., Jameson, A. G., and Humphreys, G. H.: Observations on coarctation of the aorta in infants, Arch. Surg. 86:96, 1963.

Clinical communications

Dynamics of left ventricular emptying in hypertrophic subaortic stenosis

A cineangiographic and hemodynamic study

H. Stanley Wilson, M.D.
J. Michael Criley, M.D.
Richard S. Ross, M.D.
Baltimore, Md.

Although pressure gradients are present in both idiopathic hypertrophic subaortic stenosis (IHSS) and valvular aortic stenosis (VAS), observations on the peripheral pulse and pattern of aortic blood flow during systolic ejection contrast sharply in the two conditions. In patients with IHSS there is rapid outflow from the left ventricle in early systole as evidenced by an abnormally rapid rise in arterial pressure[1] and the ejection of a large proportion of the stroke volume in the first half of systole.[2] This rapid initial ejection has been attributed to unimpeded flow, followed by the rapid development of a functional muscular obstruction which impairs emptying after mid-systole. In VAS the pulse rises slowly throughout most of systole and flow is distributed uniformly[2] since the obstruction is organic and constant.

In the present study, contrast x-ray motion pictures were utilized to study the rate and pattern of left ventricular emptying in IHSS and to observe the ventricular events responsible for the abnormal distribution of flow. For comparison, similar analyses were made of left ventricular cineangiograms from patients with normal left ventricular function and patients with VAS.

Materials and methods

Hemodynamic and cineangiographic studies on three groups of patients were analyzed (Table I). The IHSS group consisted of 9 patients with typical clinical signs and catheterization findings of idiopathic hypertrophic subaortic stenosis,† with resting gradients of 0 to 110 mm. Hg; a pressure gradient had been provoked in the patient without a resting gradient at the time of cineangiography. The VAS group included 8 patients with gradients from 50 to 168 mm. Hg and angiographic demonstration of aortic valvular disease. Eleven patients with normal left ventricular function (*vide infra*) were used as

From the Departments of Medicine and Radiology, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Md.

Supported in part by Research Grant No. HE 05484 CV from the National Heart Institute; Undergraduate Cardiovascular Training Grant No. 5 T2 HE 260 from the National Heart Institute; Clinical Center Grant No. FR 35 from the Division of General Medical Sciences; and United States Public Health Service Career Development Award No. 5K3-HE 3795.

Received for publication March 20, 1966.

Address: Department of Medicine, The Johns Hopkins Hospital, Baltimore, Md. 21205.

†All of these patients had the physical findings of left ventricular hypertrophy, a systolic murmur at the left sternal border or apex, and a normal or fast-rising pulse. On left heart catheterization, the pressure in the left ventricle rose to a late systolic peak, at a time when the aortic pressure was declining. The aortic valve had a normal appearance on angiography in all patients in this group.

normal controls. The criteria for selection were (1) good quality contrast visualization of the left ventricle in the right anterior oblique (RAO) projection and (2) pressure recordings from the left ventricle and aorta or a systemic artery. Patients in the normal group all had competent valves, normal pressures and normal systemic cardiac output. This group included 3 patients without demonstrable heart disease, 3 patients with ostium secundum atrial septal defect, 4 with mild pure mitral stenosis (mean diastolic gradient less than 6 mm. Hg or calculated mitral orifice[4] greater than 2 cm.[2]) and 1 patient with isolated mild coarctation of the aorta.

The patients with left ventricular disease (IHSS and VAS) were all studied by transseptal[3] and retrograde[4] left heart catheterization and had one or more injections of contrast material into the left ventricle. Six of the IHSS patients had two catheters in the left ventricle at the time of cineangiography, one for the injection of contrast material and the other for the recording of pressure. Six of the normal group had direct left ventricular injections, 4 had left atrial injections, and the levogram was utilized in 1 patient after an injection into the pulmonary artery. The contrast material used was sodium and methyl glucamine diatrizoate 69 and 75 per cent, 0.5 to 0.7 ml. per kilogram injected at 6 to 8 kg. per square centimeter with a power syringe.

An 8-inch image amplifier* and 35 mm. motion picture camera† were utilized for 60-frames-per-second x-ray motion pictures which were synchronized with the simultaneously recorded pressure data by an ECG-activated metallic flag in the x-ray field. A 4-msec. x-ray pulse was delivered to each frame of the film.

Technique of analysis

The films were analyzed on a 35-mm. projector,‡ and the temporal relationships between the motion picture frames and the phases of the cardiac cycle were established. The 60-frames-per-second film

ing rate allowed timing of events to within 16.7 msec.

Tracings of the left ventricular silhouette from individual frames were made (as in Fig. 1) and the areas determined in square centimeters by planimetry. Changes in left ventricular area were considered to be directionally similar to changes in volume, but because of the difficulty of converting the irregular shapes encountered in patients with left ventricular hypertrophy to conventional geometric forms, no attempt was made to derive absolute volumes.

The areas were measured frame by frame from the onset of systolic ejection (i.e., aortic valve opening) to the frame demonstrating the smallest ventricular area. The frame preceding the onset of systolic ejection was considered to be equal to the end-diastolic area (EDA) since only isovolumetric contraction had intervened. The minimal systolic area, whether it occurred in mid-systole or end-systole, was by definition equal to end-systolic area (ESA), since there was no further change in area until the mitral valve opened at the onset of the next diastole. From the end-diastolic area and the minimal systolic area, the per cent area change occurring during systole (% Δ A = EDA-ESA/EDA) was calculated. The left ventricular emptying time (LVET)

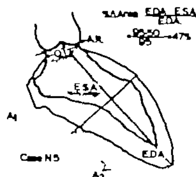


Fig. 1. Left ventricular silhouette, RAO projection, of normal patient. The end-diastolic area (*EDA*) and minimal systolic area (*ESA*) are indicated by the [illegible] and cross-hatched zones, respectively. The division of the left ventricle into subvalvular (*A1*) and apical (*A2*) areas [illegible] on the long axis is demonstrated. The aortic ring (*AR*) and minimal diameter of the outflow tract (*OT*) are also indicated. The formula for calculation of % Δ A is shown.

*Picker X-ray Mfg. Division, Cleveland, Ohio.
†Arriflex 1, B.S. Arriflex Corp. of America, New York, N. Y.
‡Tage Arno RG-35, Copenhagen, Denmark.

Table I

Patient			Diagnosis	Resting gradient (mm Hg)	ED 1 (cm)	ED 1 / ED 1 ( )	ES 1 (cm)	ES 1 / ES 1 ( )	% Δ 1
Idiopathic Hypertrophic Subaortic Stenosis									
H 1	J E	43 W M	IHSS	110	101	61 / 41	54	43 / 11	58
H 2	R E	38 W M	IHSS	47	107	62 / 45	27	26 / 1	75
H 3	E F	42 W F	IHSS	0*	75	46 / 29	31	23 / 8	59
H-4	P W	58 W M	IHSS	31	117	76 / 41	43	36 / 7	63
H 5	D R	27 W M	IHSS	1	88	58 / 30	47	40 / 7	47
H-6	L L	30 N F	IHSS	73	85	53 / 32	28	25 / 3	67
H 7	J M	16 W M	IHSS	60	72	43 / 29	37	26 / 11	49
H-8	G I	35 W F	IHSS	40	71	47 / 24	23	22 / 1	68
H 9	I M	21 W F	IHSS	61	70	49 / 21	22	22 / 0	69
		M	(IHSS)	48					62
Valvular Aortic Stenosis									
V 1	C F	44 W F	VAS	168	104	60 / 44	51	39 / 14	49
V 2	J R	45 W M	VAS	112	103	64 / 39	31	31 / 0	70
V 3	G A	54 N F	VAS	70	89	60 / 29	10	10 / 0	89
V-4	M I	22 W M	VAS	141	106	61 / 45	54	41 / 13	49
V 5	E M	33 W M	VAS	68	109	65 / 40	26	26 / 0	77
V-6	A W	41 W M	VAS	76	125	70 / 55	64	48 / 16	49
V 7	C R	45 W M	VAS	93	112	68 / 44	31	30 / 1	73
V-8	S M	10 W F	VAS	50	54	36 / 18	23	20 / 3	57
		Mean	(VAS)	97					64
Normal Left Ventricles									
N 1	A.O	24 W F	Normal	—	79	49 / 30	21	20 / 1	73
N 2	S.S.	41 W F	Normal	—	67	42 / 25	28	26 / 2	57
N 3	D.C.	17 W M	Coarct.	—	95	53 / 42	65	36 / 29	32
N-4	E.K.	34 W F	ASD	—	77	44 / 33	26	23 / 3	66

*Gradient present after isoproterenol stimulation

EDA End-diastolic area. EDA_1 EDA_2: Subvalvular (A_1) and apical (A_2) areas at end-diastole (see Fig. 1). ESA End-systolic area. $\%_{\Delta}A$ = EDA ESA/EDA × 100. $\%\Delta A_1$ $\%\Delta A_2$ Per cent change in subvalvular (A_1) and apical (A_2) areas—$\%\Delta A_1$ = EDA_1 – [illegible] Beat-to-beat interval. ( ) indicates interval in postectopic. O.T./A.R.: Outflow tract/aortic ring diameter. (l/w): Ratio of length [illegible] aortic stenosis. Coarct.: Coarctation of the aorta. ASD Ostium secundum atrial septal defect. MS Mitral stenosis.

Table I—Cont'd on pp. 8 9

%ΔA %ΔA	LVET (msec.)	%ΔA / LVET (%/msec.)	SEP (msec.)	LVET / SEP	O T / A R	(l/w)	R R (sec.)	C.O (L./min.)
30 74	170	34	320	53	66	2 2	(88)	5 7
58 98	250	30	350	71	75	3 8	92	—
50 76	135	44	250	54	1 00	4 2	80	—
53 83	200	32	270	74	90	2 2	48	3 2
29 73	170	28	210	81	1 00	1 1	54	9 1
53 91	170	39	270	63	88	5 9	50	5 0
40 62	130	37	220	60	70	4 2	(44)	—
49 96	230	30	310	74	1 00	2 6	(1 06)	3 6
35 100	170	10	260	66	74	1 1	63	4 4
46 84	180	35	273	67	85	3 0	69	5 5
36 70	315	15	360	87	1 00	7 3	96	2 0
52 100	270	26	320	84	89	1 6	88	5 1
83 100	220	40	280	79	1 00	1 3	1 08	3 5
33 71	240	21	270	89	1 00	3 8	64	—
63 100	200	36	220	91	1 00	2 7	62	8 0
31 71	260	19	320	81	1 00	3 6	(92)	4 4
56 98	230	31	315	73	81	2 7	80	4 9
41 83	230	25	280	82	1 00	3 4	72	3 8
50 87	246	27	296	83	96	3 6	83	4 5
59 96	230	32	250	92	1 00	2 3	(90)	4 7
37 90	170	33	240	71	1 00	2 6	54	—
32 31	250	13	290	86	1 00	2 6	90	—
48 91	200	33	260	77	88	2 0	60	—

([illegible] systolic area). [illegible] Subvalvular (A_1) and apical (A_2) areas at end-systole (see F[illegible]) [illegible] Percent area change— [illegible] × 100. LVET Left ventricular emptying time. %ΔA/LVET Rate of emptying. [illegible] EP Systolic [illegible] period. R R [illegible] width at end systole ([illegible] et al.[illegible]). C O Cardiac output. IHSS Idiopathic hypertrophic subaortic stenosis. VAS Valvular

Table I—Cont d

Patient			Diagnosis	Resting gradient (mm Hg)	ED 1 (cm)	ED 1 / ED 1 (cm)	ES 1 (cm)	ES 1 / ESA (cm)	% ΔA
N 5	J I	16 W M	ASD		95	59 36	50	38 12	47
N-6	E K	4 W F	ASD		76	4 34	57	30 27	25
N 7	M G	42 W F	Mild M		92	45 47	57	34 23	38
N-8	J P	34 W F	Mild MS		9	52 40	37	30 7	60
N 9	H M	47 W M	Mild MS		7	44 28	50	34 16	31
N 10	N R	40 W F	Mild MS	–	101	60 41	54	41 13	47
N 11	E M	21 W M	Normal	—	77	46 31	45	37 8	42
Mean (normal)									47

was designated as the time from the opening of the aortic valve to the first frame demonstrating minimal left ventricular area. The per cent area change divided by the left ventricular emptying time (% Δ A LVET) provided an index of mean emptying rate. The systolic ejection period (SEP) was determined as the interval between ascending and descending *intersections of superimposed left ventricular* and aortic or systemic artery tracings from a control period prior to cineangiography. In some cases SEI was determined from the actual systole studied cineangiographically since in 6 of the patients with IHSS the pressure was recorded in the left ventricle during cineangiography through a second catheter.

In order to study the dynamics of the apex and outflow tract individually an arbitrary division of the ventricle was undertaken (Fig 1). The long axis of the end-diastolic silhouette was divided perpendicularly at its midpoint and this line of division was superimposed on all subsequent frame silhouettes. The contrast area above or distal to this line of division at any time in systole was termed the subvalvular (outflow) area (A_1), the area below or proximal was termed the apical area (A_2). The per cent systolic change in A_1 and A_2 (% Δ A_1 = EDA_1-ESA_1 EDA_1, % Δ A_2 = EDA_2-ESA_2 EDA_2) was also calculated.

The diameter of the narrowest point in the outflow tract (O T) during contraction (taken as the narrowest point in the ventricular silhouette proximal to which there was a wider point) was measured and compared to the diameter of the aortic ring (O T A R). The ratio of length to width *at the time of minimal systolic area (l w)* was also measured for comparison with the data obtained by Klein and associates.

Area measurements were made by two authors independently. In instances in which there was more than a 10 per cent difference in values the measurements were repeated and a joint decision was reached.

Results

The results are given in Table I and summarized in Table II. Individuals with idiopathic hypertrophic subaortic stenosis (IHSS) as well as those with valvular aortic stenosis (VAS) achieved greater reduction of left ventricular area during systole than did the normal controls (averages of 62 and 64 per cent Δ area as opposed to 47 per cent Δ area for the normal patients $p < .05$). Although the IHSS group displayed more generalized reduction of area than that of the normal controls there was no disproportionate re

% ΔA % ΔA	LVET (msec)	% ΔA / LVET (%/msec)	SEP (msec)	LVET / SEP	O T / A.R.	(l/w)	R R (sec)	C.O (L/min)
36 67	220	21	240	92	1 00	2 9	68	4 2
29 21	200	13	230	87	1 00	1 8	64	4 1
24 51	200	19	280	71	1 00	2 4	72	2 1
42 83	260	23	280	93	1 00	2 5	88	4 4
23 43	200	15	250	80	1 00	3 0	64	5 0
32 68	200	23	260	77	1 00	2 0	70	6 7
20 74	170	25	260	65	1 00	2 8	76	8 3
35 65	209	23	258	81	99	2 4	72	4 9

Table II Summary of results

	IHSS (9)	Normal (11)	VAS (8)
Per cent area change (%ΔA)	62 (±9 3)	47 (±13 6)	64 (±15 1)
%ΔA (subvalvular)	46	35	50
%ΔA (apical)	84	65	87
Left ventricular emptying time (LVET)	180 msec. (±40)	209 msec. (±25)	246 msec (±35)
Mean rate of emptying (ΔA/LVET)	.35%/msec. (±.05)	.23 %/msec (±.09)	.27 /msec (±.09)
Systolic ejection period (SEP)	273 msec.	260 msec.	296 msec
Per cent of SEP required for emptying (LVET/SEP)	67 (±10)	81 (±9)	83 (±6)
Outflow tract/aortic ring (O T./A.R.)	.66-1.00 (.85)	.84-1.00 (.99)	.81 1.00 (.96)
End-systolic length-to-width ratio (l/w),	3 0	2 4	3 6
Heart rate	87	83	72

duction of area in the outflow tract (A) to suggest functional obstruction The time required for left ventricular emptying (LVET) was shorter in the IHSS group (average 180 msec. p = 05) and longer in the VAS group (average 246 msec. p < 05) than that observed in the control group (average 209 msec.) Hence the rate of emptying (% Δ A/LVET) was more rapid in the IHSS group (average .35 per cent per millisecond) than that in the normal (average 23 per cent per millisecond p < 01) or the VAS (average 27 per cent per millisecond p < 05) groups. Despite a slightly longer average systolic ejection period the per cent of the SEP required for achievement of minimal systolic area (LVET/SEP × 100) was less in the IHSS patients (average 67 per cent) than that observed in the normal patients (average 81 per cent, p < .01) This was in contrast to the VAS patients, in whom 83 per cent of a longer average SEP was required for emptying Heart rates although variable were comparable among the three groups (averages 87 in IHSS group 83 in normal group 72 in VAS group)

Fig 2 compares curves of area ch (in square centimeters) versus time

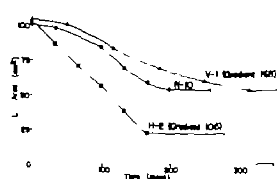


Fig. 2 Ventricular emptying curves from individual patients in the three groups. The case numbers refer to the patient in Table I. The left ventricular (LV) area is plotted against time in milliseconds throughout the systolic ejection period. The patient with IHSS (H 2) had a gradient of 106 mm Hg and yet the ventricle emptied quite rapidly to a small cavity size. The ventricle of the patient with VAS (V 1 gradient of 168 mm Hg) emptied slowly throughout a long systolic ejection period.

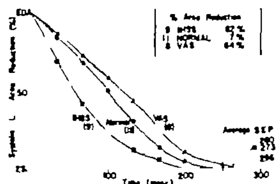


Fig. 3 Composite ventricular emptying curves from the three groups of patients. Total systolic area reduction (EDA − ESA, see Fig. 1) is expressed as per cent on the ordinate and time in milliseconds is shown on the abscissa. Each symbol represents the mean percentage of total systolic area reduction at a point in time (triangles = 8 patients with VAS; circles = 11 normal patients; squares = 9 patients with IHSS). The mean systolic ejection period (S.E.P.) for each group is indicated. These curves demonstrate the more rapid rate of emptying of the IHSS group as contrasted with the slower rate of the patients with VAS. At a point in time representing one half of the S.E.P. for each of the respective groups, the IHSS patients have achieved 85 per cent of their total systolic area reduction, whereas the VAS and normal groups have achieved about 60 per cent. The values for %ΔA (see box) indicate that emptying in the IHSS group is more complete, as well as more rapid, than in the normal group.

patient with idiopathic hypertrophic subaortic stenosis (peak Ao-LV gradient of 106 mm Hg), 1 patient with severe valvular aortic stenosis (peak Ao-LV gradient of 168 mm Hg), and a typical normal subject. The IHSS ventricle contracts rapidly to a very small area, despite the gradient of 106 mm Hg within the left ventricle. This is in sharp contrast to the VAS ventricle, which diminishes in area slowly over a large portion of a long systolic ejection period.

The sequential measurements of area throughout systole in the three groups are summarized in Fig. 3. The IHSS group has a more rapid rate of systolic area reduction than that of the normal group, *in contrast to the delayed emptying of the* VAS group. Since systolic area reduction in the IHSS group is even greater in terms of per cent area change than that in the normal group (box, Fig. 3), it can be seen that the ventricle in IHSS patients empties more *rapidly* and *completely* than in the normal patients. On the other hand, the ventricle in patients with valvular aortic stenosis is capable of complete emptying but over a longer period of time. It is important to note that the rate of emptying in the IHSS group remains rapid until a greater than normal degree of emptying is achieved, i.e., there is no point at which it could be said that ejection is delayed or prevented.

In Fig. 4 the left ventricular and aortic pressure tracings of an IHSS patient are shown on the same time scale with the left ventricular area curve. At a point 100 msec. after the onset of systolic ejection (2), about 60 per cent of total area reduction has occurred and the pressure in the left ventricle begins a sharp rise which continues for over 80 msec. During this period of rapid rise the aortic pressure falls, and the remainder of ventricular emptying is achieved. By the time the maximum pressure differential is reached 180 msec. after aortic valve opening, no further reduction in ventricular area is taking place and only the small cavity within the outflow tract itself remains as a dead space. The catheter that is recording high left ventricular pressure is not within an area of the ventricle prevented from emptying by obstruction but rather in an obliterated portion of the ventricular cavity.

In Fig. 5 the left ventricular and aortic pressure tracings of a VAS patient are

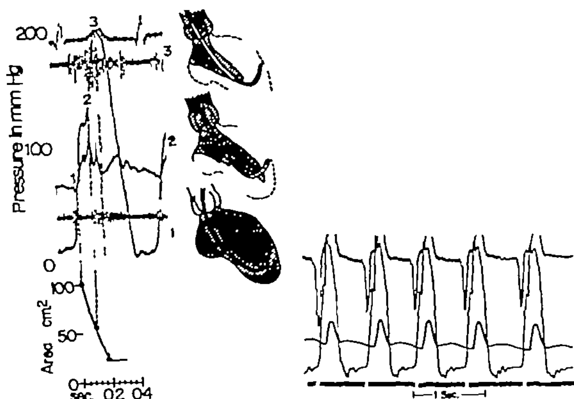


Fig. 4. The relationship of pressure gradient to left ventricular emptying in IHSS. Left ventricular and aortic pressure recordings taken immediately before cineangiography are matched with appropriate cineangiographic silhouettes and left ventricular area measurements. The upper phonocardiogram was recorded through the fluid column in the aortic catheter. The lower tracing was a chest wall phonocardiogram from the cardiac apex. The actual recordings of left ventricular and brachial arterial pressures during cineangiography are shown at the right. Pressure and cineangiographic events at the time of valve opening (*1*), 100 msec. later (*2*), and at the time end-systolic area is achieved (*3*) are correlated. Between *1* and *2* there is a rapid ventricular ejection characterized by a fast-rising aortic pulse and a marked diminution in ventricular area. Ventricular emptying is nearly complete in the first 100 msec. Between *2* and *3* the ventricular pressure rises rapidly at a time when aortic pressure is falling, and the remainder of ventricular emptying occurs. The end-systolic area (*3*) is reached before the time of peak pressure difference and a gradient persists throughout the remainder of the SEP. The marked disparity between the rising left ventricular pressure, on the one hand, and the falling aortic pressure and decreasing flow on the other indicates that the left ventricle and aorta are not in free communication during this portion of systole. If this phenomenon resulted from subvalvular narrowing, the obstruction would have to be nearly complete, yet no significant obstruction is demonstrable. It can be seen, however, that the catheter that is recording high pressure in *2* and *3* is in an emptied portion of the ventricle (*see text*). The intra-aortic phonocardiogram (*upper tracing*) reveals peak murmur intensity at point *2* during the period of rapid ventricular emptying; the murmur diminishes in intensity in late systole as flow diminishes. The aortic closure sound is delayed beyond the end of measurable ejection. Cineangiograms revealed that the aortic valve leaflets did not completely close until the left ventricular pressure fell below aortic pressure. The apical phonocardiogram (*lower tracing*) records a late systolic murmur. Intracardiac left atrial phonocardiograms (*not shown*) registered a murmur of similar characteristics.

shown on the same time scale with the left ventricular area curve. After 100 msec. of systolic ejection (*2*) only 34 per cent of systolic area reduction has taken place and the aortic pressure is rising slowly to a peak near the end of the systolic ejection period. At the time of the peak pressure difference, 160 msec. after the opening of the aortic valve, 62 per cent of systolic area reduction has occurred and the rate of area change is at a maximum. The minimal systolic area is not reached until near the end of the long systolic ejection period (*3*).

When different gradients were measured during cineangiography in the same IHSS patient in postectopic beats or beats after isoproterenol stimulation increased gradi-

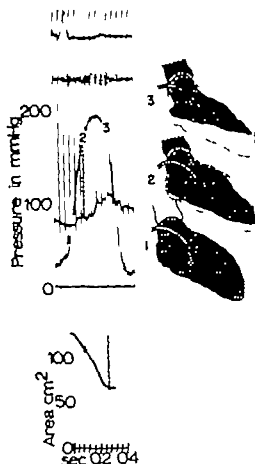


Fig. 5 The relationship of pressure gradient to left ventricular emptying in VAS. Left ventricular and aortic pressure recordings taken immediately before cineangiography are correlated with appropriate cineangiographic silhouettes and left ventricular area measurements at the time of aortic valve opening (1) 100 msec later (2) and at the time end-systolic area is achieved (3). Between 1 and 2 there is a rapid rise in left ventricular pressure which is not paralleled by aortic pressure because of the fixed obstruction at the aortic valve. There has been a 34 per cent reduction of left ventricular area during this period. At 160 msec. the maximal pressure gradient is achieved and there has been a further 30 per cent decrease in left ventricular area. The end-systolic area is not reached until 260 msec.(3). After 3 left ventricular systolic pressure rapidly declines, and there is a fall in aortic pressure.

ents were associated with more rapid ventricular emptying in 5 of 6 instances (Table III and Fig. 6).

Analyses of the patterns of ventricular contraction of the subvalvular (A_1) and apical (A_2) areas in the patients with IHSS revealed no disproportionate reduction in the outflow tract area at any time during systole. Nor was there any disproportionate subvalvular contraction when beats with higher gradients were compared with control beats in the same individual (Tables I and III).

Measurements of the narrowest point in the outflow tract of the individuals with IHSS expressed as a percentage of aortic ring diameter gave values of 66 to 100 per cent (average 85 per cent). This degree of narrowing equivalent to a 28 per cent reduction of aortic orifice area occurred late in systole after emptying had already taken place and would be expected to produce a gradient of less than 20 mm Hg even at maximum flow rates.[4] No evidence was seen of the complete closure of the subvalvular orifice postulated by Pierce and associates[3] to explain the phenomenon of a persistent pressure differential after flow ceases. In 4 of the 9 IHSS patients (H 1, H 6, H 7, H 9) left anterior oblique cineangiograms were also obtained. Measurements of the diameter of the outflow tract in this projection also failed to reveal significant narrowing during systole.

Ratios of length to width of the end systolic ventricular silhouette[4] in IHSS did not differ from the normal values [see (l/w) Tables I and II].

Discussion

This study was undertaken to compare the functional anatomy of IHSS with normal and obstructed (VAS) ventricles. It is acknowledged that the population of normal patients utilized in this study does not represent a cross section of normal individuals but ventricular function was judged to be unimpaired by hemodynamic and cineangiographic criteria. In most of the parameters studied the ventricle of the IHSS group was significantly different from that of the other two groups. In all respects studied the IHSS ventricle differed from the normal. Only in the degree of emptying (% Δ A) did IHSS resemble VAS, i.e., there was a greater than normal change in area during systole in both groups. However, the time necessary for emptying (LVET) and the rate of emptying (% Δ A/LVET) clearly separated the IHSS and VAS groups. The time required

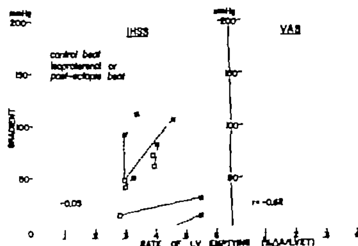


Fig 6 The relationship of the peak pressure gradient to left ventricular emptying rate (%ΔA/LVET) The pressure gradient in millimeters of mercury is on the ordinate, and the rates of emptying for the two groups are on the abscissa. There is no apparent correlation between the two parameters in the IHSS group However when individual patients had pressure gradients of different magnitude during cineangiographic studies (*joined by dotted lines*), as a result of infusion of isoproterenol or postectopic beats (*solid squares*) there was an increased emptying rate associated with increased pressure gradients in 5 of 6 instances (*see Table III*). In the VAS group there was an inverse relationship between the height of the pressure gradient and the rate of emptying—the more severe the obstruction, the slower the emptying

for the left ventricle to empty (LVET) in the IHSS group is shorter and the rate of emptying is more rapid than in either the VAS or the normal group (Fig 3 Tables I and II)

Interestingly the VAS ventricle was capable of a normal rate of emptying by the parameters used in this study (Tables I and II) Although the absolute time required for emptying (LVET) was greater in VAS the more complete degree of emptying (% Δ A) resulted in a normal value for emptying rate (% Δ A/LVET) It can be concluded that in VAS the hypertrophic ventricle is capable of a normal rate of emptying even though a significant obstruction exists however there is an inverse relationship between the rate of emptying and the left ventricular–aortic pressure gradient (Fig 6)

In contrast, the hypertrophic ventricle in IHSS empties at a more rapid than normal rate and when higher gradients were observed in the same individual as a result of isoproterenol or postextrasystolic potentiation the rate of emptying was even more rapid (Fig 6) This rapid emptying rate is reflected in the sharply rising arterial pressure[1,2] and rapid early aortic flow[3,4] observed in this disease. The cineangiographic studies serve to emphasize, however that the distribution of flow over early systole is a manifestation of early complete emptying rather than outflow obstruction in mid-systole.

The absence of a rise in arterial pulse pressure in the beat that follows an extrasystolic contraction has been considered to be a useful diagnostic sign in idiopathic hypertrophic subaortic stenosis, and the phenomenon has been attributed to increased severity of obstruction due *to augmented contraction of the outflow* tract. The current study provides evidence that ventricular emptying is enhanced rather than impaired by postextrasystolic potentiation and adrenergic stimulation. These findings fail to explain the smaller pulse pressure in the postextrasystolic beat and another explanation must be invoked Rackley and co-workers, in volume studies based on biplane cine angiograms from a patient with hypertrophic subaortic stenosis, have shown an increased ventricular stroke volume in the postextrasystolic beat. There was however increased mitral regurgitation and presumably no rise in forward stroke volume We have also noted enhanced mitral regurgitation in postextrasystolic beats and after isoproterenol If the forward stroke volume remains the same in a

Table III *IHSS Varying gradients in the same patient*

Patient	*Situation*	*Gradient*	*EDA* (cm²)	*EDA₁* *EDA* (cm²)	*ESA* (cm²)	*ESA* *ESA* (cm²)
H 5 D R 27 W M	Control	12	88	58 30	47	40 7
	After isoproterenol postectopic	31	78	47 31	27	23 4
H 3 E F 42 W F	Control	0	75	46 29	30	23 7
	After isoproterenol postectopic	12	80	53 27	20	18 2
H 2 R.E. 38 W M	Control	47	107	62 45	27	26 1
	Postectopic	95	109	63 46	27	26 1
	After isoproterenol postectopic	106	102	62 40	22	22 0
H-8 G F	Control postectopic	40	71	47 24	23	22 1
	After isoproterenol postectopic	49	71	47 24	20	19 1
H 9 L.M	Control	61	70	49 21	22	22 0
	Postectopic	82	76	50 26	23	23 0

Aortic pulse pressure in postectopic as compared to normal sinus beat ↑ = increase; ↓ = decrease; 0 = no change.
Note: Abbreviations as in Table I and text.

postectopic beat, the arterial pulse pressure will be expected to fall or remain the same (but not increase) since the volume of blood in the systemic arteries at the onset of systole is less than it is during sinus rhythm because of the increased duration of diastolic runoff. Since mitral regurgitation was augmented by the postectopic contractions, a fall in forward stroke volume could occur despite a larger change in ventricular area. The mechanism of the increased mitral regurgitation is not known, but we postulate that the normal relationship of the mitral leaflets, chordae, and papillary muscles is distorted by the rapid and complete ventricular emptying.

In none of the 9 patients with idiopathic hypertrophic subaortic stenosis could outflow obstruction capable of the production of a significant gradient be observed angiographically. Although simultaneous biplane cineangiocardiograms would be required to rule out a zone of narrowing in the outflow tract, sequential studies in RAO and LAO projections in 4 IHSS patients revealed no constriction in either projection. The pattern of contraction of the subvalvular area compared with that of the apical area was not significantly different between individuals with IHSS, those with VAS, and those with normal left ventricular function. In particular, there was no disproportion

% ΔA	% ΔA % ΔA	LVET (msec)	% ΔA / LVET (%/msec)	SEP (msec.)	LVET / SEP	O.T. / A.R.	R.R. (sec)	C.O. (L/m)	ΔPulse pressure
47	29 73	170	28	210	81	1 00	54	9 1	
66	51 90	120	55	180	67	1 00	(.42)	15 5	†
59	50 76	135	44	250	54	1 00	80	—	
74	66 91	135	55	240	56	1 00	(.60)	—	‡
73	58 98	250	30	350	71	75	92	—	
75	59 98	250	30	400	63	75	(1 20)	—	0
78	63 100	170	46	280	61	84	(.80)	—	‡
68	49 96	230	30	310	74	1 00	(1 06)	—	†
72	57 96	215	33	280	77	1 00	(.9)	—	0
69	55 100	170	40	260	77	74	63	4 4	
70	54 100	170	41	320	53	74	(.86)	—	†

ately rapid decrease in the subvalvular area or delay in apical emptying to suggest outflow obstruction.

The small ventricular area achieved in mid-systole at the time ejection ceases provides a strong argument that the ventricle is not prevented from emptying by an obstruction. In many of the cineangiograms, the only remaining ventricular volume at the time of production of the maximum gradient was in the outflow tract itself—the remainder of the cavity had been completely obliterated. Approximately 40 per cent of the circumference of the left ventricular outflow tract is made up of mitral valve and hence complete emptying of this region by contraction is anatomically untenable—a certain "dead space" is invariably present.

It has been proposed that the high ventricular pressures measured in patients with IHSS result from sustained contraction in obliterated portions of the left ventricular cavity.[1] The hypertrophic ventricles in the patients with IHSS contain many deep intertrabecular recesses which empty rapidly after the onset of systole. These recesses, as well as the entire apex of the ventricle, can often be seen to engulf the tip of the catheter (Fig. 4). After these areas become obliterated, the remainder of the ventricle continues to empty. Hence there is an early phase when there is rapid emptying without a significant gradient

(Fig 4 *1* to) a middle phase during which emptying is completed and there is a developing pressure gradient (*2* to *3*) and a late phase in which there is a pressure gradient with no further emptying (after *3*) It is suggested that this phenomenon is responsible for the pressure gradients within the left ventricle in all patients in whom obstruction is not clearly demonstrated by other means.

Summary

1 Left ventricular cineangiograms of 9 patients with idiopathic hypertrophic subaortic stenosis were studied with reference to rate and pattern of left ventricular contraction and compared with similar studies of 11 normal subjects and 8 patients with valvular aortic stenosis

2 The ventricle in idiopathic hypertrophic subaortic stenosis emptied more completely and in less time than did the unobstructed normal ventricle The left ventricle in valvular aortic stenosis emptied more completely than did the normal but required a significantly longer time interval

3 Increased pressure gradients in the same IHSS patient after premature beats or after isoproterenol were associated with more rapid and complete ventricular emptying rather than evidence of increased obstruction

4 In no case was significant narrowing of the left ventricular outflow tract seen in the RAO projection Additional LAO views were obtained in 4 patients, and no narrowing was seen There was no distinguishable difference in the pattern of subvalvular versus apical contraction between the three groups to suggest outflow tract obstruction in the idiopathic hypertrophic subaortic stenosis group—i e. neither early subvalvular contraction nor delayed apical emptying were seen.

5 These data provide evidence that the pressure gradient in idiopathic hypertrophic subaortic stenosis is not due to obstruction in those patients in whom obstruction is not clearly demonstrated by other means.

Seven of the patient with IHSS tilized in thi tudy were previously reported on in the paper by Criley nd it will be noted that the level of pressure gradients recorded differs in the two publications The pressure gradients the current report ere those recorded during cineangiography and differ in some cases from the basal values previously reported.

REFERENCES

1 Brachfeld, N and Gorlin, R : Subaortic stenosis A revised concept of the disease, Medicine 38:415 1959
2. B unwald E., Lambrew C T Morrow A. G Pierce G. D Rockoff S. D and Ross, J J Idiopathic hypertrophic s baortic stenosis, American Heart Association Monograph No. 10, New York 1964 American Heart Association
3 Hernandez R R Greenfield, J C Jr and McCall, B W Pressure-flow tudies in hyper trophic subaortic tenosis, J Clin. I vest. 43:401 1964
4 Gorlin, R and Gorlin S.: Hydraulic formula for calculation of the area of the tenotic mitral valve, other cardiac valves, and central circulatory shunts, Am Heart J 41 1 1951
5 Brockenbrough, E. C. Brau wald E., nd Ross, J J Transeptal left heart catheterization A review of 450 studies and description of an improved technic, Circulation 23 15 1962.
6. Dotter C T Left ve tricular and systemic arterial catheterization A simple percutaneous method using spring guide Am. J Roent ge ol. 83:969 1960
7 Ross, R. S. Criley J M and Morgan R H Cineangiocardiography I mitral val disease, T A. Am Physicians 74:271 1961
8. Klein M. D Lane F J Gorlin R nd Levy R. Effect of left ventricula ize and shape upon the hemodynamics of subaortic stenosis, Am. J Cardiol. 15 773 1965.
9 Brockenbrough, E. C., Bra wald E., nd Morrow A. G.: A hemodynamic technic for the detection of hypertrophic subaortic stenosis, Circulation 23 189 1961
10. Rackley C. E. Whalen, R. E. and McI tosh, H. D Ventricular volume studies I hyper trophic subaortic tenosis, Circulation. I press.
11 Criley J M Lewis, K. B. White, R. I J and Ross, R. S. Pressure gradients without obstruction—A new concept of hypertrophic subaortic stenosis, Circulation 32:881 1965.

A technique for the indirect measurement of the velocity of induced venous pulsations

Ian F. S. Mackay, L.R.C.P.I., Ph.D., F.A.C.C.
P. Van Loon, M.D.
J. T. Campos, M.D.
Lydia de Jesus, M.D.
San Juan, Puerto Rico

Alexander[1] has in a recent review pointed out the difficulties involved in the measurement of venous function, and observed that the major problem is the lack of suitable techniques particularly for in vivo studies under physiologic conditions. He discusses the possibility of a study of the relationship between the magnitude and the rate of transmission of the venous pulse and the properties of the venous wall. He comments that "Although the potentialities of such a pulse method should not be overlooked at present it has not been developed to the point that it can be applied to the accurate measurement of venous tone." He adds however that the pulsations which normally occur in the venous system are too small in magnitude and too complex in etiology to be susceptible to this type of analysis.

The purpose of this study was to design a technique which would measure the velocity of pressure pulse waves in human veins under physiologic conditions. Since the normal venous pulsations are not suitable for such a study, it was considered that the use of artificial pulsations might prove to be more useful. Landowne[2] has demonstrated the value of such an artificial approach in the study of arterial pulse wave velocities.

Examination of the transmission time and velocity of the venous pulse wave in man appears to have been neglected. Apart from a rough estimate made by Pederson, who stated that it "amounted to a fraction of a second—generally only a few tenths," no accurate measurement appears to have been made.

The measurement of the velocity of the arterial pressure pulse has been the subject of extensive investigations,[2-4] and since this factor has been used to study changes in the physical properties of the arterial wall, it is suggested that a technique for the study of venous pulse wave velocity would have similar potentialities for the study of the veins.

Apparatus

The indirect external recording of the velocity of the pressure waves was carried out with the use of two Statham pressure

From the Departments of Physiology and Surgery, University of Puerto Rico, San Juan, Puerto Rico.
This work was supported by United States Public Health Service Grant No. HE 07 23 and by the Puerto Rico Heart Association.
Received for publication March 7, 1966.
Address: The Medical Research Laboratories, University District Hospital, Caparra Heights Station, Caparra, Puerto Rico, 00935.

transducers (P23BC) to which were attached short lengths of rigid tubing over the ends of which rubber membranes were loosely tied to form small tambours of approximately 5 mm diameter (see Fig 1) The transducers were filled with water and connected to a reservoir placed 10 to 30 cm above the recording tambour At this pressure the rubber tambours adopted a slightly convex outward shape In the tubing close to the pressure transducer a 25-gauge hypodermic needle was inserted This ensured a constant pressure at the recording point but did not affect the recording of the rapid changes in pressure of the pulse waves (see inserts in Fig 1)

Large adjustable screw stands (D 12 Palmer) combined with horizontal adjustment attachments (D 14 Palmer) were found to be the most effective and steady supporting systems for the transducers. A universal force-displacement transducing cell (Statham UC3) may also be used with a short length of rubber tubing attached to the recording pin.

The recording of the pulse waves was carried out by means of a Tektronix oscilloscope Honeywell Visicorder or a Grass polygraph

For the mechanical induction of pulse waves a modified electromagnetic solenoid (12 volt) from a standard S U Morris Oxford gasoline pump was found to be effective

Procedure

The basis of our approach to the study of this problem was to artificially induce pressure waves in superficial limb veins and to measure externally the velocity of these pulse waves. During the measurements the intravenous pressure was set at different values by means of a venous congestion pressure cuff

The standard procedure adopted for the measurement of the pulse wave velocity was as follows Subjects were chosen who had prominent superficial veins on their arms. They were seated in a reclining chair with the arm extended and supported on a flock cushion The pressure cuff around the upper arm was inflated to approximately 40 mm Hg A suitable vein was

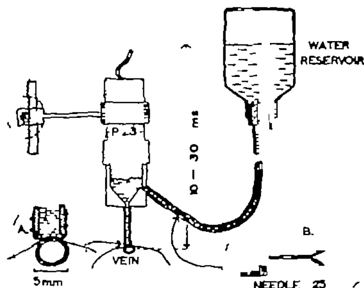


Fig 1 Diagrammatic representation of the apparatus used for indirect recording of the venous pulse wave. Attached to the Statham pressure transducers are short lengths of rigid plastic tubing over the ends of which are bound pieces of rubber to form loose tambour membranes. The whole system is filled with water and connected to a reservoir placed at a height of 10 to 30 cm, so that the rubber tambours become slightly convex. Inserted into the tube connecting the reservoir with the transducer is a narrow-gauge needle (25) which allows a constant pressure to be maintained on the tambours (see insert B), but which at the same time will not permit the loss of the sharp spike waves of the venous pulse to the reservoir Insert A demonstrates the way in which the tambours are applied to the skin.

chosen which when tapped gently displayed a visible pulse transmission Two points were chosen 5 to 15 cm apart and marked The recording instruments were lowered onto the surface of the skin directly over the veins, which was moistened with a lubricant made of glycerin jelly A heated environment was used to promote venous dilatation

The most satisfactory pressure wave was found to be a decompression or negative wave induced either digitally or mechanically The simplest way to do this was to compress the vein gently with the index finger and then suddenly lift the finger off the vessel this caused a negative pulse wave or decompression wave to travel from the point of release of digital pressure. This could also be done mechanically with the electromagnetic solenoid where a triggering mechanism could be used for the sweep of the oscilloscope ray

The digital method has an advantage in that the operator can with his tactile and pressure sensibility not only accurately locate the vein but also determine that it is compressed A skilled manipulator will produce very consistent results however positive (or compression) waves are more discretely produced by the mechanical method

A point that had to be taken into account in the standardization of the procedure was the duration of the application of the venous occluding cuff Intravenous pressure records separately made confirmed that the increase in pulse velocity is associated with a rise in intravenous pressure after the application of pressure. Two minutes were allowed to elapse from the beginning of venous congestion before a record was made in order to ensure the stabilization of venous pressure Another factor which had to be avoided was that of too prolonged venous congestion After a while the secondary waves became more exaggerated—probably because of an increase in tissue turgidity from increased accumulation of tissue fluid The measurements of velocity were made at first at lower venous congesting cuff pressures, and then in step-like fashion at suitable intervals the cuff pressure was increased The reverse order of reducing the pressure was then carried out.

The velocity of venous pulse wave transmission was calculated from the time interval between the recorded peaks of the spike-like waves.

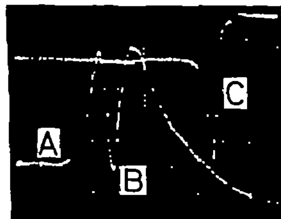


Fig 2 An oscilloscope record of typical digitally produced negative or decompression waves. The lower record (A,B) was obtained with the digital decompression applied 3 cm. from the recording point and the upper record (C) when it was applied 9 cm. from the recording point. Speed of recording 50 meters per second per division. Recording instrument Statham pressure transducer as in Fig 1 Venous congesting pressure 40 mm. Hg

Results

Fig 2 is a record from a tambour placed over the vein. The point of digital decompression was 3 cm from the tambour The record displays two components an upward broadly based deflection or positive wave (A) which is interrupted by a negative downward spike (B) This positive wave does not appear to travel as far as the negative wave for if the decompression is applied at a distance of 9 cm. from the recording point, the positive wave may be absent, as in C of Fig 2

The tissues involved in the transmission of these waves were examined by recording separately from the skin over the vein and from the adjacent tissues where no vein could be seen. The broad based positive wave appears to be transmitted via the tissues, but not so the negative spike and it is possible to subtract with a differential transducer (Statham P-23H No 113) or oscilloscope the positive wave recorded from the tissues from that ob-

tained from the vein (see Fig 3) leaving a negative spike. Tapping the veins digitally produces a positive wave (or compression wave) but even when this is done with great care the wave tends to be of a complex nature It would appear that with the induction of a negative pulse secondary waves are not so readily produced for once the device rises from the skin no further disturbance will occur whereas when the vessel is hit, it is difficult to eliminate or control the subsequent disturbance

The mechanical applicator gives pulse wave velocity results similar to those of digital compression but in addition the positive or compression spike can be more successfully produced The speed of the transmission calculated from positive or negative waves gives similar velocities. Fig 3 presents a series of records using the mechanical appliance It will be observed that after the positive wave a series of secondary waves are recorded Note also the absence of transmission of this spike wave via the tissues (Fig 3 B D E) It is interesting to note that where the negative decompression is applied no significant wave transmission is recorded from the tissues.

Fig 4 presents records obtained from intravenous needles. Here the character of the pulse waves recorded is similar although the spike tends to be rounded This is probably due to the resistance of the bore of the needles (18 gauge)

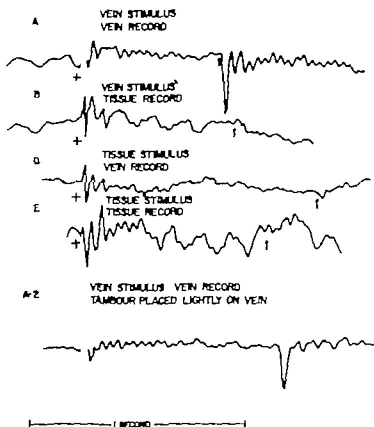


Fig 3 These records were produced with an electromagnetic applicator They illustrate two points first that the vein is the optimum route by which the spike waves travel, and second that less disturbance from tissue waves is caused when a negative or decompression wave is induced. The plus sign indicates the point at which the compression stimulus was applied the arrow indicates the point at which the decompression stimulus was applied. Recorded on Visicorder (Honeywell).

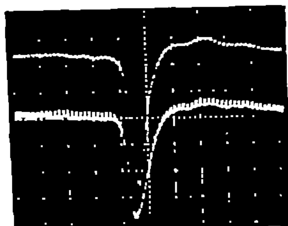


Fig 4 Simultaneous digitally induced decompression pressure pulse w es recorded from intra enous needles (20 gauge) placed 6 cm. part. Allowing for difference in length of recording tubes elocit calculated t 6.4 meters per second t cuff pressure of 40 mm Hg Speed of record 50 meters per second per division.

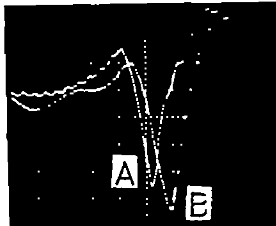


Fig 5 Simultaneous record of ... corded indirectly from the surface ... after digital decompression A w ... tambour ttached to a Statham ... (P23BC), and B was obtained fr ... displacement transducer (C2 ... instance the speed of re ord ... second per division Venous ... 40 mm. Hg Velocity of pu ... second From the peak ... records t different venou ... calculated the relationship ... locity to intra enous pr... presented I Fig 6.

Records from an intravenous needle show that negative spike waves alone are recorded from decompression of the vein, and not when the tissues are decompressed in a similar manner Similarly a positive pulse wave can be induced and recorded It appears that no significant secondary pressure waves can be recorded from the intravenous needle when the tissues are stimulated

Fig 5 presents a typical record of negative waves recorded from two transducers. It is from the peaks of these waves that the velocity of the transmission of the venous pulse waves are calculated The graph in Fig 6 was constructed from a series of such records and measurements at different venous congesting pressures.

The only natural peripheral venous pulsation the velocity of which we could indirectly measure was the "a wave of the jugular phlebogram This was done with the subject in a head-down position in which case the pressure in the vein in the antecubital region was directly measured and found to be 21 cm. H_2O By using special indirect recording equipment *it was possible to record simultaneously* the "a" wave in the neck and in the arm. The velocity was calculated from the peaks of the "a waves (see Fig 7)

Venous pulse wave velocities were mea



Fig 6 The ... ities calcula... digitally ind... results are ... cious ... tion.

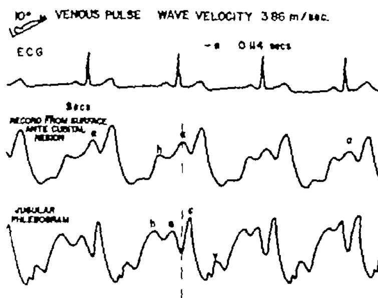


Fig 7 Indirect records of pulse waves from the jugular phlebogram and from the antecubital region. They demonstrate the time of transmission of the wave. Recorded on Grass polygraph.

sured in 20 subjects (23 to 83 years of age) in an ambient temperature of approximately 80°F. A rectilinear relationship was found between pulse wave velocity and venous congesting cuff pressure. At the lower pressures (20 mm Hg) the mean value of the pulse velocity was 4 meters per second. At the higher pressure (80 mm Hg) it was 13 meters per second.

Discussion

The first problem which had to be examined was the validity of the suggestion that the negative wave was a pulse pressure wave and not some transmitted vibration of another nature.

The most effective route for the transmission of the pulse was found to be via the vein. When the recording tambour is placed on the tissues the spike like wave is either absent or very markedly reduced (see Fig 3). Digital compression of the vein between the point of stimulation and the recording tambour prevents its transmission but not if the obstruction is placed on the tissues. Again stimulating the tissues and recording from the surface of the vein is relatively ineffective in producing the spiked pulse. Examination of intravenous records demonstrated the reproduction of the externally recorded spiked pulse waves from inside the vein but the secondary waves were absent from the intravenous record.

The velocity of the recorded pulse wave (up to 15 meters per second) suggests that it is a pressure pulse and not a flow or volume displacement. Peterson[11] recorded directly the velocity of an induced pulse wave in the veins of dogs, and found it to be 0.5 to 1.0 meters per second. This slow rate of transmission might be explained by the low natural venous pressure or it may have been a volume displacement since Caeiro[12] found a higher velocity (0.85 to 4.69 meters per second) in the same animals. The pressure spike is present in obstructed and distended vessels. The pulse wave travels along the vein in both directions and past the valves in an antidromic direction. However in an attempt to examine this problem a small roller was used to massage the blood out of the vein. The lifting of the roller from the skin allowed the vein to refill. The recorded refilling rate was much slower than that of the induced pulse wave.

A freely moving elastic tube that is stretched between two points will vibrate when a compressing agent is removed. The possibility was considered that such a movement might occur in the relatively straight superficial veins of the forearm when they are stretched by venous con

gestion. The application of positive compression with the mechanical plunger or finger where it remains in contact with the vein (and would thus dampen any vibration) produces a positive pulse wave. The pulse spike can be recorded from a vein where it has to pass around an acute angle.

There is a distinct advantage in using induced pulse pressure waves in veins. Landowne[2] has demonstrated this point in arteries. Not only are they more clearly defined but the sharp spikes are more readily measured than the complex phlebograms such as that recorded in Fig 7 where it is difficult to know what extra venous factors are involved. It is of interest to note that the velocity of the a wave of natural origin is in keeping with the velocity of the induced waves at similar pressures.

The final conclusive evidence that the spike is a pressure wave is the direct recording of the pulse wave from intravenous puncture (see Fig 4). Here the velocity and character of the pulse are in agreement with the indirect records.

Not only was indirect external recording of the pulse found to be more satisfactory in recording clearly defined spikes but it was thought that the use of intravenous needles could damage the veins and seriously alter the normality of the venous tone thus interfering with the transmission of the venous pulse. There is a further problem with puncture of the veins that of producing a hematoma when the venous pressure is raised from seepage of blood around the needle

Summary

A technique was devised for the indirect recording of the velocity of induced pressure waves in the superficial veins of the limb. The velocity of these pulse waves was measured at various intravenous pressures and compared with venous pulse waves of natural origin. These findings were confirmed by direct intravenous records. The velocity of the induced venous pulse waves in a group of normal subjects was 4 to 13 meters per second at venous congesting pressures of 20 to 80 mm. Hg

REFERENCES

1 Alexander R. S. The peripheral venous system, Chapter 31 in Handbook of physiology Section 2, Circulation, Volume 2, pp. 1090-1091 Washington D. C., 1963 American Physiological Society (Philadelphia, 1963 Williams & Wilkins)
2. Landowne, M. A method using induced waves to study pressure in human arteries, Circulation Res. 5:594 1957
3. Pederson, A. The pressure in the central veins and its bearing on peripheral venous pressure measurement, Acta Med. Scandinav (Suppl. 266) 142:879 1952.
4. Barett, H. C., and Driver N B Measurements of pulse wave velocity Am. J Physiol. 63:94 1922.
5 Crighton Bramwell, J and Hill, A. V The velocity of the pulse wave in man, Proc. Roy Soc., Ser B 93:298, 1922.
6. Wiggers, C. J Physical and physiological aspects of arteriosclerosis and hypertension Ann. Int. Med. 6 12, 193_
7 Hallock, P Arterial elasticity in man in relation to age as evaluated by the pulse wave velocity method, Arch Int. Med. 54 770, 1934
8. Haynes, F W Ellis, L. B and Weiss, S Pulse wave velocity and arterial elasticity in arterial hypertension, arteriosclerosis and related conditions, Am. Heart J 11:385 1936
9 Hamilton, W F Remington, J W and Dow P The determination of the propagation velocity of the arterial pulse wave, Am J Physiol 141:521 1945
10 Moret, P R. Modifications de l'élasticité artérielle avec l'âge, Bibl. Cardiol 15:40 1964
11. Peterson, L. H. Participation of the veins in active regulation of circulation Fed Proc 10 104 1951.
12. Caeiro, A. Velocidad de propagacion de las distintas ondas del pulso venoso, Rev Argent. Cardiol. 8:329 1941

Depression of artificial pacemakers by extraneous impulses

Agustin Castellanos, Jr., M.D.
Louis Lemberg, M.D.
James R. Jude, M.D.
Miami, Fla.

In advanced A-V block premature beats can depress impulse formation in idioventricular centers. Gaskell in 1883 observed that tertiary pacemakers could be slowed if some sinoatrial impulses could be conducted to the ventricles. Several years later Cushny described the alterations in idioventricular rhythmicity induced by rapid stimulation of the ventricles. The depressant effects of premature impulses on human pacemakers and their importance in the genesis of complex arrhythmias were emphasized by Pick and colleagues. Ordinary artificial pacemakers function as iatrogenic parasystoles which continuously stimulate the heart.[4] As in the case of their corresponding clinical counterparts the rhythmical rate of electrical pacemakers is not modified by the presence of extraneous impulses. Both are considered to be protected from the action of premature beats. A new type of electrical pacemaker has been introduced recently. This instrument will turn itself on an off when the situation so requires, hence the name *demand pacemaker*. An added basic feature consists of sensing automatically the presence of premature beats. Analysis of its behavior under usual as well as unusual circumstances reveals that artificial pacemakers can be modified so as to obey the same laws which govern naturally occurring phenomena. This communication deals with the various factors which can produce an alteration of impulse formation in an artificial pacemaker.

Material and methods

In our department transient transvenous demand pacemaking of the heart has been used since 1963 in the treatment of 63 patients with different degrees of A-V conduction disturbances. A miniaturized implantable type of demand pacemaker was employed in 3 cases by external attachment to a transvenous endocardial electrode. The basic features of this instrument have been presented in detail in previous communications. It will be emphasized that this pacemaker will escape whenever a preset asystolic interval has been exceeded. It will automatically stop when a natural or artificial beat occurs at a faster rate. The difference between this and other units is that the demand pacemaker can be influenced and its timetable rescheduled by an early ventricular contraction. The corresponding sensing device receives the signal from the premature

From the Department of Medicine (Section of Cardiology), University of Miami School of Medicine, and the Divisions of Electrophysiology and Thoracic and Cardiovascular Surgery, Jackson Memorial Hospital, Miami, Fla.
This study was aided by grants from the Heart Association of Greater Miami and the Florida Heart Association.
Received for publication March 23, 1966.

ventricular excitation regardless of its origin and discharges the pacemaker. In consequence, impulse formation starts anew. Ordinarily, the postextrasystolic pauses are more or less of the same length as the basic pacemaker R-R intervals.

The demand pacemaker was evaluated by studying the action of natural beats on demand rhythmicity. This was performed by a tape recording and rapid scanning of 24 hours of continuous monitoring. A second step in this study involved the analysis of the effects of artificial stimulation on the rhythmicity of the demand pacemaker by a method previously outlined.[4] This was done for the specific purpose of comparing the behavior of human pacemakers with that of artificial ones. An electronic model could be constructed which could mimic and explain naturally occurring phenomena.

Briefly, this method involved the use of a specially constructed tetrapolar catheter electrode with four terminals. Each set of two terminals was connected to two separate artificial pacemakers so as to provide independent bipolar stimulation.[8,9] At other times, both instruments were connected to the same bipolar set with the positive pole of one unit attached to the terminal which was connected to the negative pole of the second unit. One pacemaker was set to work on demand at a rate close to 60 per minute. The other instrument provided continuous electrical stimulation at a faster rate for variable periods of time. The latter unit was disconnected suddenly so as to study its after-effects on demand rhythmicity.

From the material available, seven tracings were selected to illustrate the basic differences between the demand pacemaker and the continuously operating unit. The resemblance between naturally occurring and iatrogenic phenomena will be stressed. Also included will be the presentation of certain types of arrhythmias which have no counterpart in the human heart.

Discharge of demand pacemaker by spontaneous ventricular extrasystoles. The records presented in Fig. 1 were obtained from an elderly patient with advanced A-V block. The demand pacemaker controlled the ventricles at a rate close to 59 per minute (cycle length of 1.02 sec.). The third QRS complex is a ventricular extrasystole (*Ex*) which occurs early in diastole. Its coupling measures 0.46 sec. This premature impulse discharges the artificial pacemaker so that its rhythmicity is altered. In consequence, the postextrasystolic interval is similar to the basic (artificial) R-R intervals. The same sequence of events occurs after the eleventh ventricular complex, which is an extrasystole occurring later in diastole. Fixed-rate artificial pacemakers are followed by postextrasystolic pauses which are shorter than the basic R-R distance. On the contrary, in these cases, the stimulus-to-stimulus intervals are constant and it is possible, according to the time of extrasystoles, for the postextrasystolic (artificial) beat to fall in the vulnerable phase of the spontaneous ventricular contraction. Repetitive firing can ensue. The incidence of this complication is avoided by the use of the demand pacemaker.[5-7]

Discharge of artificial (demand) pacemaker by conducted sinoatrial impulses. The regular activity of continuous pacemaking during intermittent A-V block is frequently interrupted whenever the ventricles are activated by a properly timed sinoatrial impulse. It is not rare to observe a return of A-V conduction in cases of



Fig. 1. Discharge of demand pacemaker by naturally occurring extrasystoles (*Ex*). The premature systoles occur at different moments of diastole. In this and in all other figures, time intervals are expressed in hundredths of a second, i.e., *102* = 1.02 sec.

complet A V block With the use of ordinary (continuous) pacemakers, a bizarre arrhythmia results because of the presence of a double rhythm

Fig 2 was obtained from a patient with intermittent A V block The upper strip shows the operation of the demand pacemaker at a rate of 49 per minute (cycle length of 1 22 sec) The fourth QRS complex is a ventricular capture by the corresponding sinus P wave It is somewhat premature for it occurs 1 16 sec. after the previous ventricular complex and is followed by an interval of 1 32 sec In this case the premature contraction discharged the artificial pacemaker and produced a postextrasystolic pause which is somewhat longer than the basic R R interval The lengthened pause can be explained by a slight (0 10 sec) depression of impulse formation in the artificial pacemaker The magnitude of this depression is clinically insignificant, for it would account for a change in rate from 49 to 46 per minute and is in keeping with similar postextrasystolic variations seen during spontaneous idioventricular rhythm

The bottom strip of Fig 2 was recorded from the same patient. The demand pacemaker was stimulating the heart at a rate of 56 per minute (cycle length of 1 08 sec.) The fifth ventricular complex is a fusion beat resulting from the simultaneous depolarization of the heart by the artificial pacemaker and the supraventricular impulse. The next QRS which is fully conducted from the atria occurs prematurely (R R interval of 1 02 sec.) It discharges the demand pacemaker The rate of the sinus pacemaker is faster than that of the artificial pacemaker Therefore the latter is kept suppressed as long as the natural rate exceeds the preset demand rate.

Discharge of artificial pacemaker by extraneous influences The arrhythmia presented in Fig 3 has not been described previously in the human heart. The first three beats are of sinus origin. There is progressive slowing of the sinoatrial pacemaker A fusion beat results when this slowing exceeds the preset demand escape interval (1 20 sec) The second pacemaker stimulus artifact also occurs at a similar interval from the first (1 16 sec.) The same distance also occurs between the third and fourth and between the fourth and fifth pacemaker spikes. However the pause between the second and third pacemaker beats is 1.50 sec. obviously longer than expected At first glance it can be ex

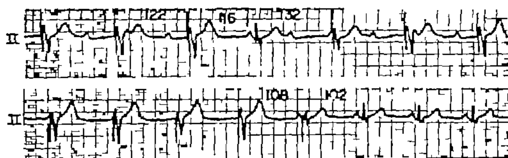


Fig 2 Discharge of demand pacemaker by conducted sinoatrial beats.



Fig 3 Artificial pacemaker escapes during sinus bradycardia There is intermittent pacemaker discharge when the P wave is superimposed in the peak of the preceding T wave. Such an arrhythmia which results from the high intensity of the sensing device, can be corrected easily The effects of blocked P waves on the automatic function of an artificial pacemaker can be considered to be one of the forms of concealed conduction—concealed atriopacemaker conduction.

plained by an irregular discharge of the pacemaker. A closer analysis, however, reveals that the T wave occurring after the second spike is taller than the rest. This is due to superimposition of T and P waves. The distance between this superimposed deflection and the next pacemaker discharge is 1.16 sec. The explanation for this unusual phenomenon is as follows: The sensitivity was set at high levels, so that the instrument sensed the taller T-P wave as if it had been a spontaneous ventricular extrasystole. In consequence, it altered the pacemaker timetable. Depression of impulse formation in an artificial pacemaker by a blocked P wave can be considered to be a heretofore undescribed form of concealed conduction[17]—concealed atriopacemaker conduction. This unusual effect was controlled by simply decreasing the sensitivity of the pickup system.

Depression of demand pacemaker by artificial stimuli. The effects of artificial stimuli on demand rhythmicity were studied by the methods described above in several patients with advanced A-V block. The upper strip of Fig. 4 shows the operation of the demand pacemaker at a rate of 57 per minute (R-R interval of 1.06 sec.). The corresponding stimulus artifacts are positive and precede each QRS complex. Artificial stimulation at a rate of 75 per minute is started toward the middle of the strip. The stimulus artifacts from this pacemaker are negative. The continuous pacemaker was suddenly shut off toward the middle of the lower strip. The distance between the last continuous and the first demand beat (asystole interval) more or less equals that between the two demand stimulus artifacts. It is thus proper to stress that the latter instrument was discharged but not depressed by rapid electrical stimulation.

Under certain circumstances, rapid electrical stimulation can produce a true depression of the demand pacemaker. This occurred whenever both instruments were connected to the same bipolar set of the catheter electrode. The top strip in Fig. 5 shows the rhythmical function of the demand pacemaker at a rate of 65 per minute (R-R interval of 0.92 sec.). The corresponding stimulus artifacts are negative. The fifth ventricular complex is a spontaneous ventricular extrasystole which is followed by a postextrasystolic pause of 1.00 sec. Artificial stimulation at a faster rate discharges the demand pacemaker (end of upper strip). The stimulus artifacts produced by this pacemaker are positive. Cessation of continuous stimulation occurs toward the middle of the lower strip. It is followed by an asystole interval of 1.58 sec., evidently longer than the distance between demand stimulus artifacts. This represents a depression of impulse formation amounting to 0.66 sec.

Marked depression of automaticity in an iatrogenic pacemaker after artificial electrical stimulation is seen in Fig. 6. The records were obtained with the same arrangement as in Fig. 5. Significant depression of impulse formation in a demand pacemaker by a single artificial extrasystole is presented in this strip. The demand pacemaker was controlling the heart at a rate of 60 per minute (R-R interval of 1.00 sec.). The fourth QRS complex is preceded by a positive-stimulus artifact. This beat, which originated from a second artificial pacemaker, occurs 0.97 sec. after the last demand-stimulus artifact. It produced a marked depression on the latter

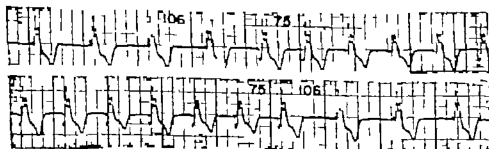


Fig. 4. Discharge of demand pacemaker by second, continuous pacemaker.

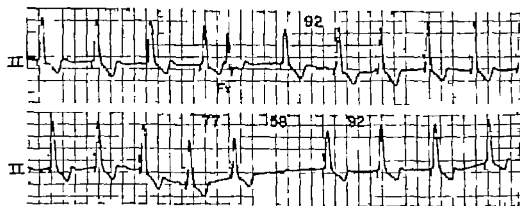


Fig 5 Discharge of demand pacemaker by natu al extras tol es od by fa ter rtificial pacemaker (*upper strip*) Cessation of timulation by the continuous pa emaker resulted depression of demand a tomaticity (*lower st p*). Figs. 5-7 were obtained under conditions which are not likely to occur during the clinical use of pacemaki g on demand



Fig 6 Depression of demand tomaticity l y single beat from another rt ficial pacemaker The resulting pause is terminated by a naturally occurring escape which precedes the rei ltution of demand ctivity

pacemaker for it is followed by a very long asystole which is terminated by a naturally occurring idioventricular escape The depression of impulse formation is still present during the first demand cycle for its duration is 1 11 sec Thereafter the pacemaker discharges at its expected rate

The first four beats in Fig 7 are preceded by positive-stimulus artifacts. They were produced by a continuous pacemaker which had interrupted the slower demand rate. The distance between each two spikes is 0 99 sec. When this unit was disconnected abruptly a prolonged interval of asystole well exceeding the demand discharge rate (R R intervals of 1 01 sec.) occurred It can be noted that the rate of the latter pacemaker increases progressively until it finally attains normal values. This warming up of an artificial pacemaker may be an iatrogenic example of Gaskell's rhythm of development as applied by Pick and associates[3] to the human heart.

Comments

The majority of the available artificial pacemakers (fixed rate units) with the exception of the atriosynchronized pacemaker unit of Nathan and co-workers,[11] deliver electrical impulses which pace the heart continuously A double rhythm results whenever the artificial stimuli coexist with isolated or multiple extrasystoles or in cases in which a regular sinus rhythm is re-established In such instances, the artificial pacemaker will function as an iatrogenic parasystole[4] yielding a ventricular response whenever the corresponding stimulus artifacts fall outside the refractory period of the previous contractions.[10] The natural beats will not alter the regular rate of discharge of this instrument. This protection from extraneous impulses is a fundamental feature of parasystole either natural or iatrogenic. On the contrary the demand pacemaker is influenced by premature impulses, for it can be discharged by single beats or by any rhythm occurring at a faster rate. In such cases the protecting mechanism is absent hence this instrument cannot be considered to be parasystolic. Its function resembles more that of idioventricular escapes, because it will stimulate only after a variable period of asystole has been exceeded This interval rhythm produced

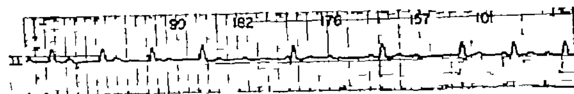


Fig 7 Depression of demand automaticity by single beat from second, electrical, pacemaker The latter part of the strip shows warming up of an artificial pacemaker (Gaskell' rhythm of development).

by the demand pacemaker is, however automatic for a re-entry phenomenon cannot be implied in its genesis. The unit under evaluation is a classic example of an iatrogenic automatic nonparasystolic pacemaker

Depression of automaticity induced by premature impulses has long been known to occur in the vertebrate heart. The effect of electrical stimulation on the automaticity of the idioventricular pacemaker in complete A V block has been a matter of considerable study by electrophysiologists.[13-14]

The introduction of electrical pacemakers for the treatment of A V block has offered adequate opportunities to study certain parameters in man which up to that moment had been observed only in the experimental animal.[19] These secondary gains obtained from the use of electronic equipment should not be considered to be of only academic interest.[17] On the contrary they can provide accessory information which can be used in the management of patients. For instance in patients with advanced A V block, interruption of an idioventricular rhythm by rapid electrical stimulation is known to produce a marked depression of automaticity.[3-4] Inhibition of impulse formation thus induced is dependent on several factors. It is more marked when the artificial rate is fast and when carried out for longer periods of time.[22] The asystole interval is longer when the patient has recently recovered from an Adams-Stokes attack due either to ventricular fibrillation or cardiac standstill.[22] This is in keeping with the well-known fact that in animals the depressant effect is more pronounced if the preparation exhibited a hypodynamic state of the cardiac muscle or a decline in spontaneous rhythmicity.[3]

Furthermore control R R intervals are not re-established immediately after cessation of electrical stimuli they require a period of time during which there is gradual buildup of automaticity to prestimulation levels.[24] According to Pick and associates, Gaskell's rhythm of development (terminology employed by experimental physiologists) actually represents a process of gradual cessation of inhibition of the idioventricular pacemakers by spontaneous rapid ventricular rhythms, with subsequent depression of the former Pick and associates[3] suggested that this mechanism might be a potential cause of Adams-Stokes syndrome in patients with advanced A V block, as in the cases reported by Cohn and Lewis[23] and Wenckebach and Winterberg.[25] Pick and associates[3] also presented the various types of natural centers which could be depressed by premature contractions.

The tracings shown in Figs. 5 and 6 demonstrate that, under certain unphysiological" conditions created purposely artificial pacemakers can also be depressed by extraneous influences. Normally the demand pacemaker is discharged but not markedly suppressed by premature beats. Depression does not always occur when it coacts with a second artificial unit. In fact, one of the indications for the use of the instrument is the intermittent failure of an implanted pacemaker.[1-] In this case, the demand pacemaker will take over only during the periods of failure of an implanted unit, thus preventing the unnecessary competition between two electronic instruments that otherwise would occur Depression of demand rhythmicity was seen under completely different conditions such as when both instruments were connected to the same bipolar set.

Discharge of an artificial pacemaker by a blocked P wave had not been described previously The arrhythmia presented in Fig 3 is considered to be an example of concealed atriopacemaker conduction. It

is the iatrogenic counterpart of a most interesting electrophysiologic phenomenon which has been of help in understanding otherwise unexplained events occurring in clinical electrocardiography.[17] This minor inconvenience can be promptly corrected during the use of portable units by simply reducing the sensitivity. The possibility that this can occur, however, has to be taken into consideration when the sensitivity of the implantable unit is being set.

The conditions under which the experiments were performed are of no clinical significance for they are not to be found during the treatment of patients. The demand pacemaker has yielded consistent results when employed properly.[5-7] The tracings presented in this communication strongly emphasize that the operation of the demand pacemaker is fully understood mainly through a thorough knowledge of the behavior of natural centers of impulse formation. This knowledge has been of help in explaining the mechanism of the various complex iatrogenic electrical arrhythmias. The use of electronic equipment has also corroborated the importance of the deductive method in the analysis of arrhythmias occurring in the mammalian heart.

Summary

Analysis of iatrogenic electrical arrhythmias serves to validate the assumptions postulated through the study of clinical electrocardiograms. Other disorders of rhythm without clinical counterpart, have also become apparent. The recently introduced demand pacemaker functions as a pacemaker that is artificial and automatic, yet not parasystolic. Ordinarily premature beats discharge but do not significantly depress the pacemaker rhythm. Under specifically induced abnormal conditions, the rhythmical discharge of this unit can be depressed by electrical impulses originating in another instrument. In this sense the function of the demand pacemaker is identical to that of other natural centers of impulse formation. For instance artifically induced Gaskell rhythm of development also seems to result from a gradual cessation of inhibition of automatism as predicted by Pick and associates from the study of clinical arrhythmias.

The analysis of artificial arrhythmias presented in this communication helps to clarify the clinical use of the demand pacemaker. This instrument has specific indications and when properly used is a valuable adjunct in the treatment of intermittent A-V block.

REFERENCES

1. Gaskell, W. L.: On the innervation of the heart with special reference to the heart of the tortoise, J. Physiol. 4:43, 1883.
2. Cushny, A. R.: Stimulation of the isolated ventricle with special reference to the development of spontaneous rhythm, Heart 3:257, 1911-1912.
3. Pick, A., Langendorf, R., and Katz, L. N.: Depression of cardiac pacemakers by premature impulses, Am. Heart J. 41:49, 1951.
4. Soloff, L.: Iatrogenic parasystole and interpolated premature ventricular beats, Am. Heart J. 63:563, 1962.
5. Lemberg, L., Castellanos, A., Jr., and Berkovits, B. V.: Pacemaking on demand in A-V block, J.A.M.A. 191:12, 1965.
6. Castellanos, A., Jr., Lemberg, L., Gosselin, A., and Berkovits, B. V.: El Marcapaso por Demanda. Un nuevo instrumento para el tratamiento del bloqueo A-V, Arch. Inst. Cardiol. Mexico 35:420, 1965.
7. Castellanos, A., Jr., Lemberg, L., and Berkovits, B. V.: The use of the demand pacemaker in atrioventricular conduction disturbances, J. Cardiovas. Surg. 7:92, 1966.
8. Castellanos, A., Jr., Lemberg, L., and Gosselin, A.: Double artificial ventricular parasystole. Iatrogenic arrhythmia for the study of excitability and conductivity in the human heart, Cardiologia 47:273, 1965.
9. Castellanos, A., Jr., Lemberg, L., Johnson, D., and Berkovits, B. V.: The Wedensky effect in the human heart, Brit. Heart J. 28:276, 1966.
10. Linenthal, A. J., and Zoll, P. M.: Quantitative studies of ventricular refractory and supernormal periods in man, Tr. A. Am. Physicians 75:258, 1962.
11. Nathan, D. A., Center, S., Wu, C. Y., and Keller, W.: An implantable synchronous pacemaker for the long-term correction of complete heart block, Am. J. Cardiol. 11:362, 1963.
12. Erlanger, J., and Hirschfelder, A. D.: Further studies on the physiology of heart block in mammals, Am. J. Physiol. 15:153, 1905.
13. Cushny, A. R., and Matthews, S. A.: On the effects of electrical stimulation on the mammalian heart, J. Physiol. 21:213, 1897.
14. Woodworth, R. S.: Maximal contraction, staircase contraction, refractory period and compensatory pause of the heart, Am. J. Physiol. 8:213, 1902.
15. Hering, H. E.: Nachweis der Automatie der Kammern bezieh ngsweise Verbid ngsfasern des Saugetthierherzens durch Auslosung ven trikularen Extrasystolen, Pflügers Arch. ges. Physiol. 108:267, 1905.

16. Lewis, R and Oppenheimer B. S.: The influence of certain factors upon asphyxial heart block, Quart. J Med. 4 145, 1911.
17 Scherf, D and Schott, A: Extrasystoles and allied arrhythmias, New York 1953, Grune & Stratton, Inc.
18. Castellanos, A. J Aran Cano, L., Calviño, J M., nd Taquechel, N: Acción de los focos ectópicos sobre los centros utomáticos del corazón, Rev Cubana Cardiol. 16:119 1955
19 De Saint Pierre G., Cammelli, L., and Pozzi R. Studio sulle modalita di resveglio dei segnapassi ventricolari in letargo, Folia cardiol. 22:393 1963.
20. Yormak, S. S., Killip, R Levit, B., and Roberts, J Depression of ventricular pacemaker by induced tachycardia, Clin. Res. 13:529 1965
21. Rothberger C. J and Winterberg, H Über extrasystolen mit kompensatorischer P use bei Kammerautomatie und über die Hemmungswirkung der Extrasystolen, Arch. ges. Physiol. 146:385 1912.
22. Edelist, A., Langendorf, R Pick, A., and Katz, L. N. Physiologic and pharmacological studies in Stokes-Adams disease patients during the use of artificial cardiac pacemaker Effect of rapid stim lation on inherent rat of spontaneous cardiac pacemakers, Circulation 28 710 1963.
23 Bredikis, Y I and Kostenko, I G.: Atrial rhythm in patients with the Morgagni-Adams-Stokes yndrome before and during electrical timulation of the heart, Bjull. Eksper Biol. i Med. 55 19 1963.
24 Castellanos, A. Jr Lemberg L. Sommer L. and Berkovits, B. V Changes i ventricular automaticity drug induced nd exposed by intracardiac electrical timulation, South. M J 58 1517 1965
25 Cohn A. E. nd Lewis, T: Auricular fibrillation and complet heart block a description of a case of Adams-Stokes syndrome including the post mortem examination, Heart 4 15 1912 1913
26. Wenckebach, K. F nd Winterberg H. Die unregelmässige Herztätigkeit, Leipzig 1927 Wm. Engelman
27 Langendorf R and Pick, A. Concealed conduction. Further evaluation of a fundamental a pect of propagation of cardiac im pulse, Circulation 13:381 1956.

The significance of the atrial situs in the diagnosis of positional anomalies of the heart

I Anatomic and embryologic considerations

*R. M Shaker M B Ch B M R C P E.**
J W Duckworth M B Ch B M.D
G H Khoury M B Ch.B
C A F Moes M D
Toronto Canada

The subjects of dextrocardia meso-cardia and levocardia have been extensively discussed Shaher and Johnson[1] found that the lesions which occur in isolated dextrocardia are the mirror image of those which occur in isolated levocardia and thought that separate consideration of them increases the confusion in an already complicated situation Several classifications for levocardia and dextrocardia have been suggested with no general agreement.[2-4] The object of this paper is to propose a simple approach to the problem of diagnosing positional anomalies of the heart. This approach stresses the anatomic and embryologic significance of the atrial situs in identifying these anomalies The angiocardiographic findings in a group of 29 patients with positional anomalies of the heart is reported in the second part of this paper [4]

Situs solitus and situs inversus hearts

When the viscera and the heart are normally situated the venous atrium is situated on the right side of the chest, and the apex of the heart is situated on the left side This type of heart is the normal situs solitus heart. When there is situs inversus totalis, the venous atrium is situated on the left side of the chest, and the apex of the heart is situated on the right. This type of heart is the normal situs inversus heart.

The normal development of the situs solitus heart is as follows (Fig 1) the dilated termination of each vitelline vein joins the caudal extremity of the endocardial heart tube. Each dilatation is joined by the corresponding umbilical vein to form the right or left primitive sinus venosus which later receives the termination of the common cardinal vein of the same side. The cranial end of the heart tube continues on each side with the first aortic arches which join the corresponding dorsal aortae. After the disappearance of the mesocardium the primitive heart is fixed to the pericardial wall only at the venous entrance or caudal end and arterial outlet or cranial end The primitive heart now undergoes differential expansion so that several dilatations separated by grooves result. These dilata-

From the Departments of Paediatrics, Radiology and Anatomy University of Toronto, and the Research Institute of the Hospital for Sick Children. Toronto, Ont., Canada.
Aided by grant from the Ontario Heart Foundation.
Received for publication March 28, 1966.
*Address: Department of Cardiology Hospital for Sick Children, 555 University Ave., Toronto 2, Ont., Canada

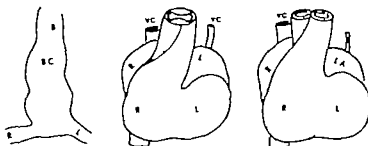


Fig. 1. Schematic representation of the various stages of the normal development of the situs solitus heart. *Left*. The straight heart tube. *Center*. Formation of the bulboventricular loop. *Right*. Completion of division of the conotruncus with the aorta arising from the left ventricle and pulmonary artery from the right ventricle. *LB* Aortic bulb. *AO* Aorta. *BC* Bulbus cordis. *IVC* Inferior vena cava. *LV* Left ventricle. *PA* Pulmonary artery. *RA* Right atrium. *RSVC* Right superior vena cava. *RV* Right ventricle. *V* ventricle.

tions from the caudal end are the right and left sinus venorum the right and left primitive atria (which soon fuse to form a single atrium) the ventricle and the bulbus cordis. Since the venous and arterial ends are fixed by the pericardium an elongation of the cardiac tube which is more rapid than the enlargement of the pericardial cavity causes the heart to bend into a compound S-shaped curve which nearly fills the pericardial cavity. Since the loop involves mainly the dilatations of the ventricles and the bulbus cordis it is called the bulboventricular loop. This loop has two limbs a dextroventral formed by the bulbus cordis which gives rise to the right ventricle and to the outflow tracts of the two ventricles and a sinistrodorsal represented by the primitive ventricle which gives rise to the left ventricle.[7] The convexity of the bulboventricular loop is directed toward the right, and its concavity to the left. During the development of the bulboventricular loop the apex of the heart is oriented toward the right because the convexity of the loop is also directed toward the right. At a later stage of development the apex of the heart has a left-sided position. With continuing growth of the cardiac tube the bulboventricular sulcus (conoventricular flange) becomes reduced in depth and the bulbus gradually shifts toward the left and appears in a midline position on the ventral surface of the developing heart. The medial shift of the bulbus is of great importance in bringing the septa in the truncus arteriosus and the bulbus cordis into line with the muscular interventricular septum. During development of the atrial septum the sinus venosus is absorbed into the right atrium and the pulmonary veins into the left atrium. At a time when the atrial and muscular ventricular septa are being formed there is a concentration of the endocardial cushion tissue into two longitudinal ridges extending into a clockwise spiral path from the cephalic end of the truncus throughout the bulbus cordis to the ventricles. The spiral septum divides the cephalic end of the truncus into two regions a sinistrodorsal which is in continuity with the sixth aortic arch (main pulmonary artery) and a dextroventral which is in continuity with the fourth aortic arch (the aortic arch). The direction of the caudal end of the spiral septum is similar to that of the muscular portion of the interventricular septum i.e. facing anteriorly and to the right, and posteriorly and to the left. In this way the sixth aortic arch which is in a dorsal position is in continuity with the right ventricle in a ventral position and the fourth aortic arch which is in a ventral position is in continuity with the left ventricle in a dorsal position.

The normal development of the situs inversus heart (Fig. 2) is exactly the same as that of the situs solitus heart, except that the relationships are reversed. Thus, the sinus venosus is absorbed into the left sided atrium and the pulmonary veins into the right sided atrium. The bulboventricular loop develops with a convexity

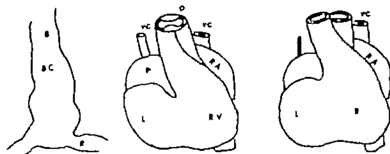


Fig 2 Schematic representation of the various stages of the normal development of the situs inversus heart *Left* The straight heart tube *Center* Formation of the bulboventricular loop. *Right* Completion of division of the conotruncus with the aorta arising from the right-sided morphologic left ventricle, and the pulmonary artery from the left-sided morphologic right ventricle. (*Abbreviations as in Fig 1*)

to the left and a concavity to the right.[7] The sinistroventral part gives rise to the right ventricle and the bulbus cordis, whereas the dextrodorsal part gives rise to the left ventricle. During development of the bulboventricular loop the apex of the heart is oriented toward the left because the convexity of the loop is also directed toward the left.[7] At a later stage of development the apex of the heart has a right-sided position The aorto-pulmonary septum separates the fourth arch sinistroventrally from the sixth arch dextrodorsally With complete development of the spiral septum the sixth aortic arch comes into continuity with the left-sided ventricle (morphologic right ventricle) and the fourth arch into continuity with the right sided ventricle (morphologic left ventricle)

Positional variation of the apex of the heart

From the very beginning the atria are fixed to the posterior body wall by the entering veins and by the persistent portion of the mesocardium [7] On the other hand the apex of the heart is not a fixed structure and can move from right to left or remain in the midline. In its final stage of development the situs solitus heart has the morphologic right atrium on the right and the morphologic left atrium and cardiac apex on the left. The early bulboventricular loop of this heart points toward the right but later takes a left sided position If the apex remains on the right, there is dextroversion of the ventricles. If it remains in the midline, there is mesocardia with solitus atria and if it takes a left sided position we speak of the normal situs solitus heart (Fig 3) Developmentally therefore dextroversion of the ventricles, mesocardia with solitus atria and the normal situs solitus heart are one and the same in so far as orientation of the chambers and great vessels is concerned The essential feature of this group is a morphologic right atrium on the right and a morphologic left atrium on the left.

The situs inversus heart in its final stage of development has the morphologic right atrium on the left and morphologic left atrium and cardiac apex on the right The early bulboventricular loop of this heart points toward the left but later takes a right-sided position. If the apex of this heart remains on the left there is levoversion of the ventricles if it remains in the midline, there is mesocardia with situs inversus atria and if it takes a right-sided position we speak of the normal situs inversus heart (Fig 3) Developmentally therefore levoversion of the ventricles mesocardia with situs inversus atria and the normal situs inversus heart are one and the same in so far as orientation of the chambers and great vessels is concerned The essential feature of this group is a morphologic right atrium on the left and a morphologic left atrium on the right.

From the aforementioned three types of dextrocardia mesocardia and levocardia exist (1) those with a morphologic right atrium on the right and a morphologic left atrium on the left (2) those with a morphologic right atrium on the left and a morphologic left atrium on the right

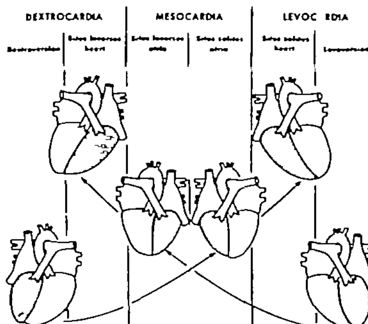


Fig 3. Positional variation of the pex of the normal situs solitus and situs i ersus hearts. Arrows indicate the direction of shifting of the cardiac apex during normal development. Note the occurrence of the tw types of levocardia, mesocardia, and dextrocardia. A third type exists if the situs of the atria is not know

(3) those with an indeterminable atrial situs.

Positional anomalies of the heart

Positional anomalies of the heart in this paper refer to four conditions in which the cardiac apex is not situated on the same side as that of the morphologic left atrium (1) dextroversion of the ventricles, (2) mesocardia with situs solitus atria (3) levoversion of the ventricles (4) mesocardia with situs inversus atria.

Inversion of the ventricles

Occasionally the bulboventricular loop of a situs solitus heart may develop a convexity to the left and a concavity toward the right (Fig 4) This type of loop will have two limbs a sinistroventral which gives rise to the morphologic right ventricle and the bulbus cordis and a dextrodorsal which gives rise to the morphologic left ventricle. The morphologic right atrium on the right will communicate with the morphologic left ventricle, now situated in a dextrodorsal position, and the morphologic left atrium on the left will communicate with the morphologic right ventricle now situated in a sinistroventral position. When the bulboventricular loop of a situs solitus heart develops a convexity toward the left, congenitally corrected transposition almost always results[4] The apex of this heart initially points towards the left, but later takes a right-sided position. In other words situs solitus hearts with this type of loop, after complete development, should have dextroversion of the ventricles. If the apex of this heart fails to point to the right, and instead points to the midline or remains on the left, mesocardia with situs solitus atria and inversion of the ventricles or situs solitus heart with inversion of the ventricles will result.

The embryologic basis of inversion of the ventricles in situs inversus hearts is the same as that of inversion of the ventricles in situs solitus hearts. Thus, a heart which is going to be a situs inversus heart develops with the morphologic right atrium on the left and the morphologic left atrium on the right (Fig 5) The bulboventricular loop however develops con exity to the right and a conca ity to the left. Since the morphologic right ventricle develops on the convex sid of the loop and the morphologic left ventricle on ts concave side

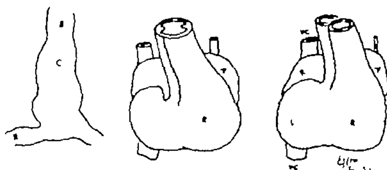


Fig 4 Schematic representation of the various stages of the development of in ersion of the entric les n itus solitus heart. *Left* The straight heart tube (note right tri m on the right and left trium on the left). *Center* Bending of the bulboventricular loop to the left *Right* Completion of the process of in ersion of the ventricles and the development of corrected transposition of the great essels the right atrium comm nicates with the morphologic left ventricle nd the left trium communicates th the morphologic right entricle the orta originates from the morphologic right entricle nd the pulmonary rtery from the morphologic left ventricle

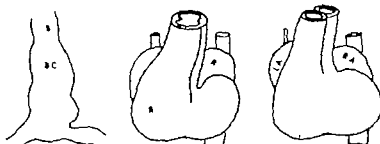


Fig 5 Schematic representation of the various stages of development of i ersion of the ventricles in situs inversus heart *Left* Straight heart tube (note right trium on the left, and left atrium on the right). *Center* Bending of the bulboventricular loop to the right. *Right*. Completion of the process of inversion of the en tricles and the development of corrected transposition of the great essels.

the morphologic right atrium (on the left) will communicate with the morphologic left ventricle whereas the morphologic left atrium (on the right) will communicate with the morphologic right ventricle Since the convexity of the bulboventricular loop is toward the right, the apex of this heart initially points toward the right but later takes a left-sided position. In other words situs inversus hearts with this type of loop should develop levoversion of the ventricles. However if the apex fails to point to the left and remains in the midline or points to the right mesocardia with inversus atria and inversion of the ven tricles or situs inversus heart with inver sion of the ventricles will result. Situs inversus heart with this type of loop almost always develops corrected transposition of the great vessels.[8]

Transposition of the great vessels

In transposition of the great vessels the aorta arises anteriorly in front of the crista supraventricularis whereas the pulmonary artery is posterior to the aorta There are two types of transposition of the great vessels in which the aorta and the pul monary artery arise from separate ven tricles. These are complete and congenitally corrected transposition When the mor phologic right atrium is situated on the right, regardless of the position of the cardiac apex complete transposition is present if the aorta communicates with the right (venous) ventricle and the pul monary artery with the left (arterial) ventricle (Fig 6) On the other hand when the morphologic right atrium is situated on the left regardless of the position of the cardiac apex complete transposition

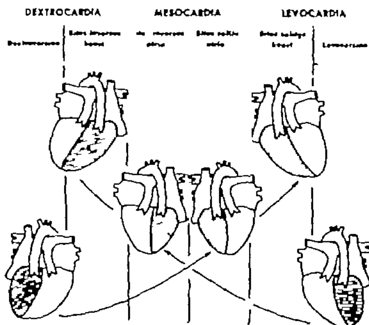


Fig. 6. Positional variation of the apex of the situs solitus and situs inversus hearts with complete transposition of the great vessels. Arrows indicate the direction of shifting of the apex of these two hearts during the various stages of development.

is present if the aorta communicates with the left-sided (venous) ventricle and the pulmonary artery with the right-sided (arterial) ventricle (Fig. 6).

When the morphologic right atrium is situated on the right, regardless of the position of the cardiac apex, *congenitally* corrected transposition is present if the aorta arises from the left-sided (arterial) ventricle and the pulmonary artery from the right-sided (venous) ventricle (Fig. 7). Similarly, if the morphologic right atrium is situated on the left, regardless of the position of the cardiac apex, corrected transposition is present if the aorta arises from the right-sided (arterial) ventricle and the pulmonary artery from the left-sided (venous) ventricle (Fig. 7).

Viscero-atrial relationship and asplenia

In the syndrome of congenital absence of the spleen, advanced abdominal heterotaxy may be present. Severe cardiac anomalies may occur and may represent abnormal septation of the conotruncus and abnormal division of the atrioventricular canal. Thus, transposition of the great vessels, pulmonary atresia, single ventricle, various anomalies of the atrioventricular valves, common atrium, and cor biloculare are features of the developmental syndrome of congenital cardiac disease and asplenia. Persistence of the left superior vena cava, absence of the inferior vena cava with drainage of the lower part of the body through an azygos vein which arises to join a right or left superior vena cava, and partial or total anomalous pulmonary venous drainage are often present.[5-]

Ivemark[1] explained the association of asplenia, abdominal heterotaxy, and conotruncal malformation of the heart by an arrest of development at the stage at which the body first searches out its normal asymmetry. He suggested that the basic developmental error with respect to the heart is in the elaboration of the cardiac jelly that gives rise to these structures. Since the anlage of the spleen arises simultaneously with elaboration of the cardiac jelly, he considered that whatever adverse forces may be responsible for dystrophy of the splenic primordia have likewise affected the heart at this early stage. Putschar and Manion[18] suggested that asplenia and heterotaxy may be due to suppression of structures that are asym-

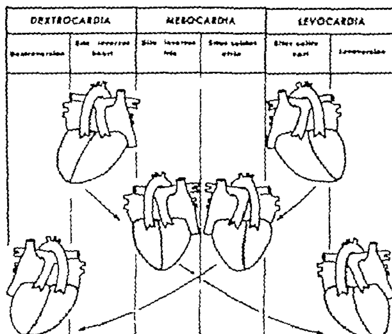


Fig. 7. Positional variation of the apex of the situs solitus and situs inversus hearts with corrected transposition of the great vessels. Arrows indicate the direction of shifting of the cardiac apex during the various stages of development. Note that either dextroversion or levoversion results if development is completed.

metrical by their left-sidedness, resulting usually in various degrees of bilateral right-sidedness. They reviewed 78 cases of asplenia and found that there was no other malformation of the abdominal viscera in 43 cases, whereas in the other 35 there was abdominal heterotaxy. Malformations of the heart occurred in 49 of their 78 cases. *Malformation of the heart alone without malformation of the viscera* occurred in 20 of the 49 cases, whereas partial situs inversus without cardiac malformation occurred in 6 cases. These findings suggest that (1) *in slightly less* than half of all cases of asplenia the visceral situs *is indeterminable*; (2) *abdominal* heterotaxy is not present in all cases of asplenia; (3) *abdominal heterotaxy with*out cardiac involvement may be present in *a few cases* of *asplenia*. Recently Van Mierop and Wiglesworth[11] pointed out that in some cases of asplenia the two atria are morphologically right atria and suggested the term isomerism of the atria to describe this condition.

Discussion

During cardiac development the position of the ventricles and that of the great vessels are subject to deviation from the normal pattern. Thus the bulboventricular loop of either the situs solitus or the situs inversus heart may develop a convexity to the right or to the left. In other words, the right ventricle of either heart may be situated on the right or on the left. Similarly, the great vessels may be transposed or both vessels may originate from one ventricle. The apex of either heart may point to the right, to the midline, or to the left. On the other hand, from the very beginning, the atria are fixed structures. *The atria are the only cardiac compartments the development of which is not affected by the shape of the bulboventricular loop.* Whether the morphologic atrium *develops on the right, as in the situs solitus* heart, or on the left, as in the situs inversus heart, it does so in the normal position for either of these two hearts.

During the course of cardiac development the apex of the heart shifts from right to left in the case of the situs solitus heart and from left to right in the case of the situs inversus heart (Fig. 3); hence the existence of two types of levocardia, mesocardia, and dextrocardia. A third type exists if the atrial situs is unknown. What

effect has the position of the apex of the heart on the anatomic diagnosis of any heart lesion? Categorically it makes little difference whether the apex of the heart is situated on the right, on the left or in the midline. On the other hand if the position of the atria is not known or cannot be determined neither the type of heart the type of transposition of the great vessels, nor the presence or absence of inversion of the ventricles can be determined The only sure way of making an anatomic cardiac diagnosis is by locating the position of the atria. During life this can be done by angiocardiography whereas at autopsy the morphologic characteristics of the atria will differentiate the right atrium from the left atrium[3]

The position of the abdominal viscera in relation to the type of heart deserves special mention Although in the majority of cases the situs of the atria corresponds to that of the abdominal viscera, and the situs of the abdominal viscera may be taken to be indicative of that of the atria,[4] there are however odd cases in which discordance between the position of these structures occurs. Here again for cardiac anatomic diagnosis, if the situs of the morphologic right atrium is known it matters very little whether the abdominal viscera are concordant or discordant. Moreover the indeterminable visceral situs in some cases of asplenia should not be a deterrant to the making of a complete cardiac diagnosis if the position of the atria is known

Many terms have been used in the literature to denote a discrepancy between the position of the apex of the heart, the type of heart, and the situs of the abdominal viscera. Although each of these terms has its own advantages and disadvantages, it is probably more revealing to use such terms which describe the position of the apex if this does not conform with that of the atria e g "dextroversion of the ventricles," levoversion of the ventricles, etc. Discrepancies between the type of heart and the situs of the abdominal viscera should be described as they occur e g situs solitus heart with situs inversus of the abdominal viscera, or situs inversus heart with situs solitus of the abdominal viscera.

Summary

Two types of heart exist the situs solitus and the situs inversus hearts. The normal development of these hearts as well as the abnormal development of inversion of the ventricles, are discussed It has been shown that the situs solitus heart mesocardia with solitus atria, and dextroversion of the ventricles are one and the same in so far as orientation of the great vessels and chambers of the heart is concerned Similarly the situs inversus heart, mesocardia with inversus atria and levoversion of the ventricles are one and the same in so far as orientation of the great vessels and chambers of the heart is concerned

Positional anomalies of the heart have been defined as those conditions in which the apex of the heart does not lie on the same side as that of the morphologic left atrium. Four conditions were identified (1) dextroversion of ventricles, (2) mesocardia with solitus atria, (3) levoversion of ventricles, and (4) mesocardia with inversus atria.

The viscero-atrial relationship is discussed and it has been pointed out that, although in the majority of cases the position of the atria corresponds to that of the abdominal viscera there are odd cases in which discrepancies between the situs of these structures occur It has been stressed that the only sure way of making an anatomic cardiac diagnosis is by locating the atria at necropsy or angiocardiographically

REFERENCES

1 Shaher R. M and Johnson, A M Isolated laevocardia and isolated dextrocardia P thology and pathogenesis, Guy Hosp. Rep. 112 127 1963.
2 Lev M and Rowlatt U F The pathologic anatomy of mixed levocardia. A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition, Am. J Cardiol. 8:216, 1961
3. Arcilla, R A. and Gasul, B. M Congenital dextrocardia, J Pediat. 58:39 and 251 1961
4 Van Praagh R. Van Praagh, S Vlad, P and Keith, J D Anatomic types of congenital dextrocardia. Diagnostic and embryologic implications, Amer J Cardiol. 13:510, 1964
5 Rosenbaum, H D A simplified basic classification of spatial alignments of the heart, its chambers and the great vessels, Circulation 30 191 1964.

6. Shaher R M Moes, C A F and Khoury C The significance of the atrial situs in the diagnosis of positional anomalies of the heart II An angiographic study of 29 patients, AM HEART J 73:41 1966.
7 De la Cruz, M V Anselmi, G Cisneros, F Reinhold, M Portillo, B., and Espino-Vela, J An embryologic explanation for the corrected transposition of the great vessels. Additional description of the main anatomic features of this malformation and its varieties, AM HEART J 57 104 1959
8 Van Mierop, L H S and Wiglesworth F W Pathogenesis of transposition complexes. III True transposition of the great vessels, Am. J Cardiol. 12:233 1963
9 Bush J A and Ainger L E Congenital absence of the spleen with congenital heart disease, Pediatrics 15:93 1955
10. Wilh, H and Gasser C The clinical diagnosis of the triad spleen agenesis, defects of the heart and vessels and situs inversus, Etudes Néonatales 4:25 1955
11 Levy D Congenital malformations of the heart and the great vessels associated with congenital absence of the spleen, Arch Dis. Child. 32 131 1957
12 Plowman, D E. M Congenital absence of spleen associated with cardiac abnormalities Brit M J 1 147 1957
13 Lyons, W S Hanlon, D G. Helmholz, H F J DuShane J W and Edwards, J E. Cardiac Clinics, CXLVIII Congenital cardiac disease and asplenia. Report of seven cases, Proc. Staff Meet. M yo Clin. 32:277 1957
14 Gilbert, E. F Nishimura, K. and Wedum, B G Congenital malformations of the heart associated with splenic agenesis, with report of five cases, Circulation 17 72 1958.
15 Grant, R P The syndrome of dextroversion of the heart Circulation 18:25 1958
16 Roberts, W C., Berry W B. and Morrow A G The significance of asplenia in the recognition of inoperable heart disease Circulation 26 1251 1962.
17 Kamal, B M Syndrome of levocardia, multiple cardiac defects, situs inversus and absent spleen. A case report, AM. HEART J 63:115 1962.
18. Ruttenberg H. D Neufeld H N Lucas, R. V Jr Carey L. S. Adams, P Jr Anderson, R C., and Edwards, J E. Syndrome of congenital cardiac disease with asplenia, Am J Cardiol. 13:387 1964.
19 Ivemark, B I Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood, Acta Pediat. 44 1955 Suppl 104
20. Putschar W G. J and Manion, W C. Congenital absence of spleen and associated anomalies, Am. J Clin. Path 26:429 1956.
21 Van Mierop, L. H and Wiglesworth, F W Isomerism of the cardiac atria in the asplenia syndrome Lab. Invest 11 1303 1962

The significance of the atrial situs in the diagnosis of positional anomalies of the heart

II An angiocardiographic study of 29 patients

R M Shaker M B Ch.B M.R C P E.
C A F Moes M.D
G H Khoury M B Ch.B
Toronto Canada

In the first part of this paper positional anomalies of the heart have been defined as those conditions in which the apex of the heart is not situated on the same side as that of the morphologic left atrium Four conditions were included (1) dextroversion of the ventricles (2) mesocardia with situs solitus atria (3) levoversion of the ventricles (4) mesocardia, with situs inversus atria.

The anatomic features and the embryologic development of these four types have been discussed in the first part of this paper

The present angiocardiographic study was undertaken first, to investigate the nature of the associated defects in positional anomalies of the heart, and second to stress the significance of assessing the position of the atria by angiocardiography as a basis for recognition of these anomalies

Material and method

Angiocardiograms in 29 patients with positional anomalies of the heart were studied in detail

An Elema-angiogram was recorded in 18 patients, and cineangiograms were obtained in the other 11 These were made in the anteroposterior and lateral projections in all but one patient in whom only a lateral view was available In 16 patients the contrast material was injected via the venous route usually from the femoral vein or with the catheter in the inferior vena cava. In 9 a selective procedure was performed with the tip of the catheter in the right ventricle or main pulmonary artery and in the other 4 both selective and venous angiograms were recorded The diagnosis was confirmed at operation in 9 cases and at necropsy in 3

Results

1 Position of the cardiac apex In this series dextroversion of the ventricles was present in 21 patients (Figs 1 and 2) Mesocardia with situs solitus atria was noted in 5 (Fig 3) Levoversion of the ventricles was encountered in 3 (Fig 4) In none was there mesocardia with situs inversus of the atria.

2 The viscero-atrial relationship In 28 patients, or in 96 per cent of the cases the position of the atria corresponded to that of the abdominal viscera. In the one other

From the Departments of Paediatrics and Radiology University of Toronto, and the Research Institute of the Hospital for Sick Children, Toronto, Ont Canada.

Aided by grant from the Ontario Heart Foundation.
Received for publication March 23 1966

Address Department of Card[illegible] for Sick Children, 555 University Ave Toronto 2, Ont., C[illegible]

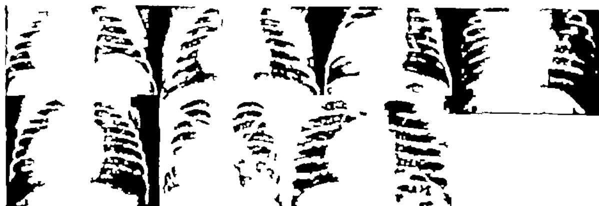


Fig 1 Chest radiographs of 7 patients with dextroversion of the ventricles and normal relationship of great vessels. Note the scimitar shadow in *F* (Case 6)

Fig 2 Chest radiographs of 14 patients with dextroversion of the ventricles and transposition of the great vessels.

patient (Case 28) discrepancies between these structures occurred In this patient the cardiac apex and stomach air bubble lay on the left side in the chest radiograph (Fig 4,*B*) whereas at cardiac catheterization the inferior vena cava and the venous atrium were found to be on the left side and the arterial atrium was on the right side (Fig 5)

3 Morphology of the atria. The right



Fig. 3 Chest radiographs of 5 patients with mesocardia and solitus atria In A B and C there was normal relationship of the great vessels, whereas in D and E there was transposition of the great vessels.



Fig 4 Chest radiographs of 3 patients with levoversion of the ventricles. In B (Case 28) the stomach air bubble lies on the left.

atrium on the angiocardiogram was seen as a vertical oblong chamber in continuity with the inferior and superior venae cavae. The vertical position was particularly noticeable on the lateral projection and contrasted markedly with the normal oblique position of this chamber (Fig 6) The left atrium was round rather than being somewhat oblong with the long diameter placed transversely as is seen in the normal heart (Fig 6) The atria lay side by side on the anteroposterior projection and were superimposed on the lateral.

4 Position and morphology of the ventricles The morphology of the ventricular chambers was difficult to recognize since both tended to be smooth walled in outline. On the anteroposterior projection the morphologic right ventricle was often triangular in shape and the medial margin was concave where it abutted against the left ventricle (Fig 6) The morphologic left ventricle was round and tended to displace the inferior aspect of the venous ventricle laterally or laterally and superiorly (Fig 6) The ventricles in all cases lay side by side on the anteroposterior projection and were superimposed on the lateral projection because of a sagittal position of the interventricular septum.

5 Aortic arch The arch of the aorta was situated on the left in every case of levoversion of the ventricles or mesocardia with situs solitus atria (Figs



Fig 5 Anteroposterior nd lateral angiocardiograms in Case 28. Not left-sided inferior vena cava (*IVC*), right-sided left trium (*LA*), a single ventricle (*S V*), transposition of the great vessels, nd pulmonary stenosis A Aorta, *PA* Pulmonary rtery



Fig 6. Anteroposterior and lateral angiocardiograms of one of the patients with dextroversion nd normal relationship of the great vessels Note the right trium (*RA*), which lies in vertical position nd the left atrium (*LA*), which appears rounded. The right entricle (*RV*) and left entricle (*LV*) have smooth outline. Both lie side by side. The pulmonary artery (*PA*) ascends long the right pper cardiac border turns medially then inferiorly to give rise to the right and left branches. The orta (*A*) ascends to the left of the pulmonary artery nd arches to the left and descends to the left of the spine.

7 and 8) In those cases of levoversion of the ventricles the arch was placed on the right and on the side opposite the cardiac apex (Fig 5)

6 Relationship of the great vessels In only 11 patients was a normal relationship of the great vessels observed Seven had dextroversion of the ventricles, 3 had mesocardia with situs solitus atria, and 1 had levoversion of the ventricles (Tables I II and III) In contrast to the normal heart, in which the pulmonary artery forms a convexity on the left upper cardiac border this structure was seen to occupy the right upper cardiac border although in some instances it was somewhat obscured by the right atrial appendage The pulmonary artery originated from the right entricle and ascended along the right upper cardiac border turned medi-



Fig 7 Anteroposterior and lateral angiocardiograms Case 8 with dextroversion and complete transposition of the great vessels. The aorta (*Ao*) arises from the right ventricle and arches to the left. The pulmonary artery (*PA*), situated posteriorly, is opacified from the aorta through a patent ductus arteriosus. Note juxtaposition of the right atrial appendage (*RAA*).



Fig 8 Anteroposterior and lateral angiocardiograms of one of the patients with dextroversion, corrected transposition, ventricular septal defect, and pulmonary stenosis. The morphologic left ventricle (*LV*) on the right gives rise to the posterior pulmonary artery (*PA*). Severe pulmonary stenosis (*PS*) is present. The ascending aorta (*Ao*) situated anteriorly opacifies from the right-sided ventricle through a ventricular septal defect. The aortic arch is on the left.

ally then inferiorly at rather a sharp angle to give rise to the right and left branches. The aorta rose from the left ventricle and ascended to the left of the main pulmonary artery then arched to the left and posteriorly to descend on the left (Fig 6) The aortic arch formed the left upper cardiac border

Transposition of the great vessels was present in 18 patients 14 had dextroversion 2 had mesocardia and solitus atria and 2 had levoversion of the ventricles (Tables I II and III) In 6, the proximal connection of the transposed arteries was established Complete transposition was present in 1 (Fig 7) and corrected transposition in 5 (Fig 8) In the other 12 the proximal connections of the great vessels, and therefore the type of transposition could not be determined Eleven of these 12 patients had additional complicated defects in the form of single ventricle pulmonary atresia or tricuspid atresia (Tables I II and III) The main pulmonary artery in the group with transposition of the great vessels was directed superiorly and did not arch inferiorly as in those with a normal relationship of the great vessels, before giving off to the right and left branches (Fig 8)

7 Associated defects The associated defects are presented in Tables I II and III and existed in all but 2 patients (Cases 1 and 2) in whom the relationship of the great vessels was normal The defects in the other 27 tended to be milder when the great vessels were normally related than when they were transposed

Table I *Associated defects in 21 patients with dextroversion of the ventricles**

Case	Name	Age	Sex	Necropsy	Associated findings
1	W W	2 yr	M	—	None
2	G W	10 y	M	—	None
3	M D	4 mo.	F	—	Preductal coarctation of aorta
4	D P	7 mo.	F	—	ASD
5	M G	3 yr	F	—	VSD
6	S. T	13 yr	F	—	ASD scimitar syndrome
7	E. A.	15 y	F	—	PDA Postductal coarctation
8.	Baby P	1 wk.	M	—	TGV SV TA, PDA
9	C. M	2 mo	F	—	TGV SV TA, PS
10	Girl K	3 mo	F	—	TGV PS VSD
11	G M	4 mo.	M	—	TGV SV PS asplenia
12.	S. S	7 mo.	F	Yes	Complete TGV PDA, juxtaposition of atrial appendages
13	G H	1 yr	M	—	TGV SV PA, PDA, ASD
14.	B C.	2½ yr	F	—	TGV SV
15	B S	4½ y	F	—	TGV SV PS
16	N B	5 yr	M	—	TGV SV PS, TA
17	R. S.	5 yr	M	—	Corrected TGV PS, VSD
18.	G V	10 yr	M	—	Corrected TGV PS, VSD
19	M B	12 y	F	—	Corrected TGV VSD left atrioventricular valve insufficiency
20.	N B	15 yr	F	Yes	Corrected TGV PS, VSD
21	D W	15 yr	M	—	Corrected TGV PS VSD

*Patients 1 7 have normal relationship of the great arteries Patients 8-21 have transposition of the great vessels.
ASD Atrial septal defect *PA* Pulmonary atresia *PDA* Patent ductus arteriosus. *PS*. Pulmonary stenosis *SV* Single ventricle. *TA* Tricuspid atresia *TGV* Transposition of the great vessels *VSD* Ventricular septal defect.

Table II *Associated defects in 5 patients with mesocardia and solitus atria*

Case	Name	Age	Sex	Necropsy	Associated finding
22	L. H	3½ mo.	M	Yes	Anomalous origin of left coronary artery from pulmonary artery EFE
23	A. L.	5 yr	M	—	Small VSD
24	C H	7 yr	F	—	PDA
25.	T R	15 mo.	M	—	TGV SV TA, PDA
26	M S.	7 yr	M	—	TGV SV TA, PA

*Patients 22-24 have normal relationship of the great arteries.
Abbreviations as in Table I. *EFE* Endocardial fibroelastosis

Table III *Associated defects in 3 patients with levoversion of the ventricles**

Case	Name	Age	Sex	Necropsy	Associated findings
27	K. H	4 mo.	M	—	SV PS, ASD
28.	Girl D	5 mo.	F	—	TGV SV PS ASD
29	P K	6 yr	M	—	TGV SV PS probable asplenia

*Patient 27 has normal relationship of the great vessels.
Abbreviations as in Table I.

Discussion

The present study demonstrates that lack of shifting of the apex of the heart to its definitive position is not an innocent anomaly. Eleven patients (38 per cent) had a normal relationship of the great vessels, and in 2 of these there were no associated defects, whereas in the other 18 (62 per cent) there was transposition. When the origin of the great vessels was from separate ventricles, corrected transposition was more common than complete transposition. The high incidence of transposition in dextroversion has been noted previously by other writers.[2,3] It is entirely possible that this increased incidence of transposition of the great vessels is due to the fact that only symptomatic patients tend to be investigated whereas those with mild lesions escape recognition. That this is probably true is suggested by the fact that at least 12 other patients seen regularly at the Hospital for Sick Children have dextroversion of the ventricles with significant symptoms or signs sufficient to warrant complete investigation. Moreover in the series of 41 patients reported by Ayers and Steinberg 9 had no associated cardiac anomalies. Corrected transposition of the great vessels was observed in 8 of their cases.

The high incidence of corrected transposition in dextroversion or levoversion has been explained by de la Cruz and associates, who pointed out that, because the initial convexity of the bulboventricular loop in corrected transposition with situs solitus atria is directed to the left, when development is completed dextroversion of the ventricles should result. Similarly in corrected transposition with situs inversus atria the initial loop convexity is toward the right with complete cardiac development levoversion of the ventricles results. It remains to be explained however why the side-to-side relationship of the ventricles in dextroversion exists.

The side-to-side relationship of the ventricles has been observed by others.[4] This may be explained by the fact that during early cardiac development the apex of a situs solitus heart shifts from right to left, and at the same time there may be a degree of clockwise rotation of the ventricles. If arrest of development occurs then a side-to-side ventricular relationship takes place. The side-to-side relationship of the atria probably results from the abnormal position of the ventricles.

In all of the present series with dextroversion or levoversion, the aortic arch was situated on the side opposite to that of the cardiac apex. This finding is probably of importance in differentiating cases of ventricular dextroversion from a situs inversus heart, and cases of ventricular levoversion from a situs solitus heart. In a few reported cases of dextroversion[4,7] and levoversion[8] however the aortic arch has been on the same side as the cardiac apex.

The association of a hypoplastic right lung a "scimitar"-shaped shadow of an anomalous pulmonary vein along the right cardiac border and dextroversion of the ventricles is now well recognized. Christmens, Dupuis and Avinée[10] studied 13 cases of dextroversion and 2 cases of mesocardia and noted that anomalous drainage of the right pulmonary veins into the inferior vena cava deserves to be pointed out. Nine of the 41 patients reported on by Ayers and Steinberg[4] had anomalous drainage of the pulmonary veins (site unspecified). Only 1 patient presented with this anomaly in the present series.

As pointed out earlier transposition of the great vessels, single ventricle, or inversion of the ventricles is relatively frequent in positional anomalies of the heart. Under such circumstances the only definite way to determine the type of positional anomaly of the heart is by determining the position of the atria. When the position of the atria cannot be determined as in some cases of asplenia, neither the type of heart, the presence or absence of inversion of the ventricles nor the type of transposition can be determined. In the majority of cases the position of the abdominal viscera as determined clinically may give a clue to the position of the atria. In some cases, however isolated inversion of the stomach occurs, and in rare instances discordance between the site of the atria and that of the abdominal viscera occurs. For these reasons we think that

the only sure way to determine the type of cardiac anomaly in positional abnormalities of the heart is by locating the venous atrium angiocardiographically.

Summary

The angiocardiograms of 29 patients with positional anomalies of the heart are presented. Dextroversion of the ventricles was present in 21, mesocardia with solitus atria in 5, and levoversion of the ventricles in 3. A normal relationship of the great vessels was observed in only 10 patients, whereas transposition was observed in 19. When the proximal connections of the great arteries could be established, corrected transposition was more common than complete transposition. Associated defects were present in 27 cases. These defects tended to be milder when the great arteries were normally related than when they were transposed. In all patients the aortic arch was situated on the same side as the morphologic left atrium. The morphology of the ventricular chambers was difficult to recognize since both tended to be smooth walled in outline. In cases in which two ventricles were present, these chambers lay side by side. The significance of assessing the atrial situs as the basis for the recognition of positional anomalies of the heart has been stressed.

REFERENCES

1. Shaher, R. M., Duckworth, J. W., Khoury, G. H., and Moes, C. A. F.: The significance of the atrial situs in the diagnosis of positional anomalies of the heart. I. Anatomic and embryologic considerations, Am. Heart J. 73:32, 1966.
2. Grant, R. P.: The syndrome of dextroversion of the heart, Circulation 18:25, 1958.
3. Van Praagh, R., Van Praagh, S., Vlad, P., and Keith, J. D.: Anatomic types of congenital dextrocardia. Diagnostic and embryologic implications, Am. J. Cardiol. 13:510, 1964.
4. Ayers, S. M., and Steinberg, I.: Dextrorotation of the heart. An angiocardiographic study of forty-one cases, Circulation 27:268, 1963.
5. De la Cruz, M. V., Anselmi, G., Cisneros, F., Reinhold, M., Portillo, B., and Espino-Vela, J.: An embryologic explanation for the corrected transposition of the great vessels. Additional description of the main anatomic features of this malformation and its varieties, Am. Heart J. 57:104, 1959.
6. Poker, N., and Steinberg, I.: Dextrorotation of the heart in rheumatic mitral stenosis, Circulation 30:907, 1964.
7. Rösler, H.: Beiträge zur Lehre von der angeborenen Herzfehlern, bei die angeborene isoliert Rechtslage des Herzens, Wien. Arch. f. inn. Med. 19:505, 1930.
8. Hickman, W.: Malformation of the heart: transposition of the ventricles and of the aorta, absence of pulmonary artery, patent foramen ovale, communicating ventricles, with lateral transposition of principal viscera, cyanosis, Tr. Path. Society London 20:80, 1869.
9. Neill, C. A., Ferencz, C., Sabiston, D. C., and Sheldon, H.: The familial occurrence of hypoplastic right lung with systemic arterial supply and venous drainage "scimitar syndrome," Bull. Johns Hopkins Hosp. 107:1, 1960.
10. Christmens, L., Dupuis, C., and Avinée, J. C.: Les dextroversions cardiaques, Arch. Mal. Coeur 57:809, 1964.

Significance of T loop change in vectorcardiographic diagnosis of left ventricular hypertrophy

Kazuhiko Murata M.D
Hiroshi Kurihara M.D
Satoru Matsushita M.D
Masao Ikeda M.D
Masuji Seki M.D
Tokyo Japan

It was suggested in our previous reports that a displacement of the T loop to the right in the vectorcardiogram might be an important clue to the diagnosis of left ventricular hypertrophy (LVH) whereas a vectorcardiographic diagnosis based solely on the magnitude of the QRS vector was not very sensitive.[1,2] Although the frequent occurrence of abnormal orientation of the T loop opposite the QRS loop in LVH has been well recognized,[3-9] the diagnostic importance of such a displacement of the T loop has not been investigated precisely. The present study was undertaken in order to evaluate the clinical significance of the T loop change in vectorcardiographic diagnosis of LVH.

Materials and methods

Studies were made on the vectorcardiograms of 175 patients autopsied either at the Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo or at the Yokufukai Geriatric Hospital. Although the patients ranged in age from 27 to 91, most of them were from the Geriatric Hospital and thus over 60 years old. Cases of intraventricular conduction disturbance and vectorcardiograms recorded at the terminal stage were excluded. Cases of right ventricular hypertrophy of more than moderate degrees at autopsy were also discarded.

The method of recording the vectorcardiogram was the same as that used in the previous studies.[1,2] The Frank lead system of electrode placement was used. The chest electrodes were placed at the level of the fifth intercostal space. The three planar projections of the vectorcardiogram were recorded simultaneously with FVC 3.† The QRS loop was interrupted either 500 or 800 times per second. The sagittal plane was viewed from the left. Measurements were made of the direction of half area QRS and maximum T vectors as well as of the magnitude of maximum QRS vectors in each plane. The magnitude of the T vector was not measured in the present study. The angles of the vectors were plotted using the notation proposed by Helm. The magnitude of

From the Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo, and Yokufukai Geriatric Hospital, [illegible], Tokyo.
Received for publication April [illegible] 1966.
Address: Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo, Tokyo, Japan.
†Fukuda Medical Electronics C[illegible] Japan.

the spatial angle between half area QRS and maximum T vector was calculated by using Helm s table [11] Although the angle between half area QRS and maximum T angle was measured in each plane the results were not included in the present study because of an abnormal distribution

The hearts were examined according to the conventional method The thickness of both ventricular walls was measured after formalin fixation excluding the epicardium endocardium and papillary and trabecular muscles The main stems and branches of the coronary arteries were sectioned at intervals of 0.5 cm According to the criteria in our laboratory anatomic diagnosis of LVH was made when (1) the heart weight was greater than 350 grams (2) the heart weight was greater than 300 grams and the thickness of the left ventricular wall was 1 0 cm. or more or (3) the heart weight was greater than 250 grams and the thickness of the left ventricular wall was 1 1 cm or more A reduction of more than 50 per cent in the diameter of the coronary artery was considered to indicate significant coronary sclerosis. Pathologic evidence of LVH was present 85 cases. The underlying disease in most cases of LVH was hypertensive or coronary heart disease Significant coronary sclerosis was present in 100 cases whereas myocardial infarction was demonstrated in 18

According to the anatomic findings in the heart, the cases were divided into the following four groups (1) normal without any significant anatomic change in the heart (2) coronary sclerosis without LVH (3) uncomplicated LVH (4) LVH with coronary sclerosis. The groups consisted of 39 51 36 and 49 cases, respectively

Results

The direction of the maximum T vector in each plane is plotted in Figs 1 and 2 and the results are summarized in Table I Illustrative T loops are shown in Figs. 3 and 4

Magnitude of maximum QRS vector The magnitude of the maximum QRS vector was greater in the cases with LVH than in the normal group whereas the figures for the group with coronary sclerosis without LVH were almost identical to those for the normal group

Maximum T angle As shown in Table I and Fig 1 the T loop was usually directed to the left inferiorly and anteriorly in the absence of LVH whereas a rightward displacement of the T loop was seen in a majority of the cases with LVH whether associated or not with significant coronary sclerosis. The maximum T angle in the frontal and horizontal planes was significantly greater in both groups with LVH than in the normal group The figures for the group with coronary sclerosis without LVH were almost the same as those for the normal group although the distribution was slightly greater in the former group

A displacement of the T loop to the right and posteriorly was seen in the cases

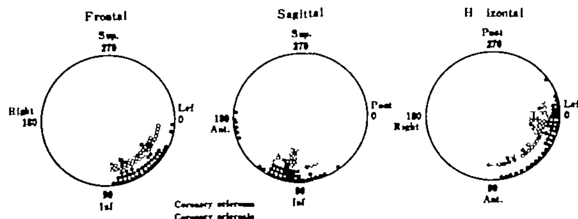


Fig 1 Direction of maximum T vector in 90 cases without left ventricular hypertrophy

of LVH associated with significant coronary sclerosis as shown in Fig. 2.

Spatial QRS-T angle. The spatial QRS-T angle was also significantly greater in both groups with LVH.

Direction of inscription of T loop. Although the T loop may be inscribed in any direction in the frontal plane, a clockwise inscription in the horizontal plane was not observed in the normal group, whereas such an abnormal direction of inscription was seen in 3 cases of the group with coronary sclerosis without LVH, in 12 cases of the group with uncomplicated LVH, and

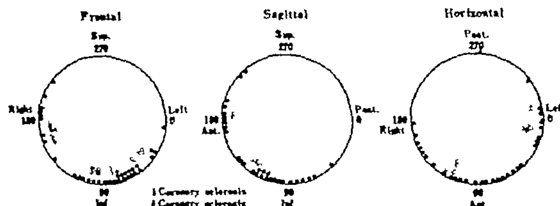


Fig. 2. Direction of maximum T vector in 85 cases with left ventricular hypertrophy.



Fig. 3. T loop of a 63-year-old man with moderate left ventricular hypertrophy. The heart weighed 340 grams. The T loop was directed to the right, anteriorly, and superiorly. Despite a marked displacement of the loop it was inscribed counterclockwise in the horizontal plane.

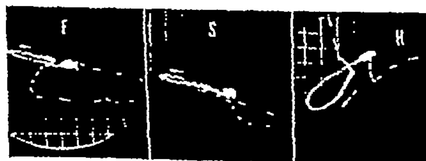


Fig. 4. Vectorcardiogram of a 36-year-old man who died of malignant hypertension. A marked left ventricular hypertrophy was demonstrated at autopsy. The heart weighed 615 grams. Note displacement of the T loop to the right, anteriorly, and superiorly and clockwise inscription of the loop in the horizontal plane.

in 12 cases of the group with LVH with coronary sclerosis. There was a close relationship between the direction of inscription of the T loop in the horizontal plane and the maximum T angle. A clockwise inscription was not observed when a T loop was directed to the left, whereas a T loop was almost always inscribed clockwise when the maximum angle was greater than 130 degrees.

Incidence of abnormal findings. The incidences of the abnormal findings in each group are tabulated in Table II. Because normal values for the Frank lead vectorcardiogram in Japanese have not been established as yet, the normal upper limit was set as mean × 2 standard deviations of the values for the normal group.

As shown in Table II, a rightward displacement of the T loop outside the normal range was demonstrated in 55.6 per cent of the group with uncomplicated LVH and in 59.2 per cent of the group with LVH associated with significant coronary sclerosis. The corresponding figures in the normal group and the group

Table I. Measurements of Frank lead vectorcardiograms of 175 autopsy cases

	Normal	*Coronary sclerosis without LVH*	*Uncomplicated LVH*	*LVH with coronary sclerosis*
Number of cases	39	51	36	49
Magnitude of maximum QRS vector (m)				
Frontal	1.28 ± 0.60	1.25 ± 0.42	1.59* ± 0.61	1.71 ± 0.78
Sagittal	0.89 ± 0.43	0.94 ± 0.33	1.26** ± 0.49	1.17 ± 0.57
Horizontal	1.16 ± 0.51	1.17 ± 0.42	1.53** ± 0.59	1.70** ± 0.70
Maximum T angle (degrees)				
Frontal	55 ± 20	53 ± 40	111 ± 53	101** ± 74
Sagittal	106 ± 27	113 ± 35	132 ± 50	126 ± 54
Horizontal	19 ± 28	22 ± 41	84** ± 57	88* ± 69
Spatial QRS-T angle (degrees)	55 ± 24	44 ± 25	95** ± 48	93** ± 48

*Borderline ($p < 0.05$)
**Significantly greater than normal group ($p < 0.01$)

Table II. Incidence of abnormal findings in Frank lead vectorcardiogram

	Normal	*Coronary sclerosis without LVH*	*Uncomplicated LVH*	*LVH with coronary sclerosis*
Number of cases	39	51	36	49
Enlarged magnitude of maximum QRS vector	3(7.7)*	5(9.8)	10(27.8)	17(34.7)
Rightward displacement of T loop	3(7.7)	7(13.7)	20(55.6)	29(59.2)
Clockwise inscription of T loop in the horizontal plane	0	3(5.9)	12(33.3)	12(24.5)
Enlarged magnitude of spatial QRS-T angle	2(5.1)	3(5.9)	17(47.2)	14(28.6)
Abnormal T loop without enlarged magnitude of QRS vector	3(7.7)	6(11.8)	13(36.1)	16(32.7)
Enlarged magnitude of maximum QRS vector without T-loop change	3(7.7)	2(3.9)	3(8.3)	4(8.2)

*Numbers in parentheses are per cent.

with coronary sclerosis without LVH were 7.7 and 13.7 per cent, respectively. A clockwise inscription of the T loop in the horizontal plane or an enlarged magnitude of the spatial QRS-T angle was seen less frequently in each group.

Although an enlarged magnitude of the QRS vector was seen with almost the same frequency as a rightward displacement of the T loop in the normal group and the group with coronary sclerosis without LVH, the former abnormality was less frequent than the latter in the cases of LVH. An isolated abnormality of the T loop in the absence of an enlarged magnitude of the QRS vector was present in 29 of 85 cases with LVH, whereas an isolated abnormal enlargement of the QRS vector was demonstrated in only 7 cases.

Discussion

Although ST-T change in the scalar electrocardiogram is a useful clue to the diagnosis of LVH, the change is not believed to be very reliable because of a rather low specificity.[13] In so far as the vectorcardiogram is concerned, some of the previous investigators did not consider the T-loop change to be an important sign for the diagnosis of LVH for the same reason.[1,17] In the present study, however, a high incidence of T loop change in the presence of LVH was *demonstrated*, whereas the possibility of false-positive diagnosis was comparatively low.

In the present series, a rightward displacement of the T loop was present in 55.6 per cent of the group with uncomplicated LVH and in 59 per cent of the group with LVH and significant coronary sclerosis, whereas such a displacement was demonstrated in only 7.7 per cent of the normal cases and in 13.7 per cent of the cases of coronary sclerosis without LVH. A rightward displacement of the T loop was seen more frequently than an enlarged magnitude of the maximum QRS vector in the cases of LVH, whereas the possibilities of false-positive diagnosis in the cases without LVH were almost identical for both parameters. The above-mentioned results apparently indicate that a displacement of the T loop to the right is a more reliable sign of LVH than was formerly believed and suggest that the maximum T angle may be a better parameter than an enlarged magnitude of the QRS vector in the diagnosis of LVH. A rather low incidence of abnormal findings in the cases of LVH in the present series, as compared to the former reports,[1,17] is probably due to the inclusion in our material of many cases of mild LVH. The magnitude of the calculated spatial QRS-T angle was believed not to be of great diagnostic importance, because a rather cumbersome calculation did not improve the diagnostic reliability. The present finding that an isolated T loop change not associated with an enlarged QRS vector was present in 37 cases of LVH disagrees with the previous observation by Bristow, who found no instance of such an isolated T-loop change in 46 cases of LVH.

In so far as the direction of inscription of the T loop is concerned, a close relationship with the direction of the maximum T vector was demonstrated, in accord with a previous report by Harumi. A clockwise inscription of the T loop in the horizontal plane was never observed when the maximum T angle was smaller than 90 degrees, whereas a T loop was usually inscribed clockwise when the maximum angle was greater than 130 degrees. The incidence of such an abnormal direction of inscription of the T loop in the LVH groups was nearly the same as the corresponding incidence of the enlarged magnitude of the maximum QRS vector, whereas no clear-cut relationship was observed between the direction of inscription of the T loop and the degree of coronary sclerosis. Although a clockwise inscription of the T loop in the horizontal plane is a very specific finding in cases of LVH, the diagnostic value of this sign seems to be limited because of low sensitivity.

An interesting finding in the present study was that a T loop directed to the right and posteriorly was not seen in uncomplicated cases of LVH. Such an unusual orientation of the T loop was observed exclusively when significant coronary sclerosis was present in association with LVH. Although the clinical significance of the posterior displacement of the T loop has not been pointed out by previous investigators, the present finding suggests that a

displacement of the T loop to the right and posteriorly is of considerable importance because such a T loop probably indicates the presence of myocardial ischemia in association with LVH

Summary

1 One hundred and seventy five Frank lead vectorcardiograms of autopsy cases were reviewed in order to evaluate the significance of T loop change in the diagnosis of left ventricular hypertrophy (LVH)

2 The T loop was usually oriented to the left and inferiorly in the absence of LVH whereas in the majority of the cases of LVH whether associated or not with significant coronary sclerosis, the T loop was displaced to the right and anteriorly A significant rightward displacement of the T loop was observed in 55 6 per cent of 36 cases of uncomplicated LVH and in 59 2 per cent of 49 cases of LVH associated with significant coronary sclerosis. The corresponding figures in the normal cases and in those with coronary sclerosis without LVH were 7 7 and 13 7 per cent, respectively

3 A T loop directed to the right and posteriorly was seen exclusively when significant coronary sclerosis was present in association with LVH

4 A displacement of the T loop to the right was considered to be a more sensitive and reliable sign of LVH than was formerly believed and the maximum T angle was thought to be a better parameter for the diagnosis of LVH than the magnitude of the QRS vector A possible clinical significance of posterior displacement of the T loop was also suggested

REFERENCES

1 Murata, K., Kurihara, H Hosoda, H Ikeda, M and Seki, M Frank lead vectorcardiogram in left ventricular hypertrophy J p. Heart J 5:543, 1964.
2. Murata, K., Kurihara, H Ikeda, M and Seki, M Vectorcardiogram in left ventricular hypertrophy—A vectorcardiographic and pathologic correlation in the aged, Acta Gerontol. J p. 11:49 1965 (In Japanese)
3. Bristow J D Porter G. A. and Griswold, H E. Observations with Frank system of vectorcardiography in left ventricular hypertrophy Am Heart J 62:621 1961
4 Burch, G. E. Abildskov J A., and Cronvich J A. Spatial vectorcardiography Philadelphia, 1953 Lea & Febiger p. 120.
5 Grishman, A and Scherlis, L. Spatial vectorcardiography Philadelphia, 1952, W B Saunders Compa y p. 70
6. Massie L. E. and Walsh T J Clinical vectorcardiography and electrocardiography Chicago, 1960, Year Book Publishers, Inc p. 125
7 Mazzoleni, A., Wolff R. and Wolff L. The vectorcardiogram in left ventricular hypertrophy Am Heart J 58:648, 1959
8. Sano, T Ohshima, H., Tsuchihashi, H and Shimamoto, T The quantitative nalysis of vectorcardiogram of normal hearts and left ventricular hypertrophy Jap. Heart J 1:226, 1960.
9 Toyama, S. Abnormal T loop in vectorcardiogram Jap. Circ. J 27:37 1963.
10. Frank, E An accurate, clinically practical system for spatial vectorcardiography Circulation 13 737 1956.
11 Helm R. A Vectorcardiographic notation, Circulation 13:737 1956.
12. Helm, R. A., and Fowler N O A simplified method for determining the angle between tw spatial vectors, Am. Heart J 61:242, 1961
13. Allenstein B. J and Mori, H.: Evaluation of electrocardiographic diagnosis of left ventricular hypertrophy Circulation 21 401 1960.
14. Mazzoleni, A Wolff R., Wolff L. and Reiner L. Correlation between component cardiac weights and electrocardiographic patterns in 185 cases, Circulation 30:808 1964.
15 Selzer A. Ebnother C. L. Packard, P Stone A. C., and Quinn, J E. Reliability of electrocardiographic diagnosis of left ventricular hypertrophy Am. Heart J 59 155 1960.
16. Scott R. C. The electrocardiographic diagnosis of left ventricular hypertrophy Am. Heart J 59 155 1960.
17 Wolff L., Wolff R., Samartzis, M D Mazzoleni, A., Soffe, A. N Reiner A. N and Matsuoka, S. Vectorcardiographic diagnosis. A correlation with autopsy findings in 167 cases, Circulation 23:861 1961
18. Harumi, K., Mashima, S. Sato, C., Yanai, Y and Ueda, H A study on the direction of inscription of the vectorcardiographic T-loop in left and right ventricular hypertrophy Jap. Heart J 4:586, 1963

Experimental and laboratory reports

Myocardial depression accompanying chronic consumption of alcohol

John E. Maines III, Ph.D.
*Earl E. Aldinger, Ph.D.***
New Orleans, La.

Ethyl alcohol has been shown to have a damaging effect on the liver;[1] however, the pharmacologic effects of chronic ingestion of ethanol on the cardiovascular system have not yet been elucidated. For some time many investigators have been aware of different clinical syndromes of heart failure associated with alcoholism. Walshe, as early as 1873, noticed an association between alcoholism and heart disease. Until recently, the pathologic effects of chronic alcoholism have usually been considered to be primarily the result of associated nutritional deficiencies. Walsh and Burch, Evans, and others have recently described the clinical features of alcoholic cardiomyopathy, in which it is thought that the excessive and habitual consumption of alcohol for many years causes injury to the myocardium. Evidence for this stems mainly from clinical observations, wherein variables, such as the intake of food and alcohol, are extremely difficult to control. Controversy still remains whether the cardiotoxicity seen in alcoholic patients is due to nutritional deficiencies associated with alcoholism or to a manifestation of the intrinsic action of ethanol itself.

The present study was designed to test the hypothesis that chronic alcoholism results in myocardial damage despite adequate intake of food.

Methods

For these experiments, 140 male Sprague-Dawley rats weighing between 280 and 390 grams were divided into four groups as follows: *Group I*, alcohol-intoxicated rats numbering 60; *Group II*, nonalcoholic control rats (40) pair fed daily with Group I and receiving an equal caloric value of dextrose; *Group III*, alcoholic rats (12) pair fed with Group I and receiving a daily vitamin supplement (2 times the minimum daily requirement); *Group IV*, normal control rats (28) receiving food and water ad libitum. Alcohol was given orally as 25 per cent ethyl alcohol by volume in water ad libitum. Each animal was placed in a separate cage with individual food cups and fluid bottles, and all animals in the first three groups received ground Purina Laboratory Chow. The normal control group was fed Purina Laboratory Chow in pellet form. Twice weekly each animal was weighed and the intake of alcohol and water was measured. The daily intake of food was measured for each animal in Group I, and the animals in

From the Departments of Pharmacology and Medicine, Tulane University School of Medicine, and [illegible] Memorial Research Laboratory, United States Public Health Service Hospital, New Orleans, La.

This work was supported by United States Public Health Service Grant Nos. [illegible] and [illegible].
The data for this publication were taken in part from a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Tulane University.
Received for publication March 4, 1966.

*Predoctoral Fellow, Department of Pharmacology, Tulane University School of Medicine. Present address: Department of Pharmacology, Bowman Gray School of Medicine, Winston-Salem, N. C.
**Associate Professor, Departments of Medicine and Pharmacology, Tulane University School of Medicine. Present address: Research Laboratory, U. S. P.H.S. Hospital, 2[illegible] State St., New Orleans, La.

Groups II and III were pair fed the same amount Water was substituted for alcohol in Group II To maintain the same caloric intake in Groups I and II dextrose was mixed with the food given to Group II in proportion to the caloric value of alcohol *consumed by Group I By grouping the* animals in this manner the intake of food and fluid was carefully controlled and the alcoholic and control animals could be compared both as separate groups and as paired samples.

Cardiovascular changes were monitored on animals from time to time in order to determine whether significant changes in myocardial function were developing Pair fed control Group II and alcohol vitamin pair fed Group III animals were reserved until significant changes in myocardial function were observed in Group I Groups II and III were then compared throughout the remainder of the study with Group I to determine the possible role of nutritional deficiency in the production of myocardial depression

All animals were anesthetized with sodium pentobarbital (50 mg per kilogram intraperitoneally) A tracheotomy was performed and artificial respiration was provided by means of a Phipps and Bird small animal rhythmic motor-driven respirator The right carotid artery and jugular vein were cannulated with poly *ethylene tubing for measurement of blood* pressure and for the administration of drugs respectively A midline thoracotomy was performed and the heart exposed for the measurement of isometric systolic tension (IST) with a strain-gauge lever system [8] The two feet of the lever system were attached with cotton sutures to an 8-mm segment of the right ventricle in a vertical plane from apex to valve. The segment of muscle between the two points of attachment was stretched so as to apply an initial tension of 8 and 12 grams above end-diastolic tension. Eight grams of tension consistently *resulted in an increase* in the tension-to-length ratio whereas 12 grams sometimes produced a decrease in this ratio Therefore the tension to-length ratio at 8 grams was always situated in the uppermost segment (80 to 95 per cent) of the *ascending* portion of the Starling curve The strength of myocardial contraction developed under these specific and designated circumstances is an indication of potential myocardial contraction [9]

Blood pressure was measured with a Statham (P23Db) transducer heart rate *with a tachometer from impulses taken* from the IST recordings and the electrocardiogram from Lead II All parameters were recorded on a Sanborn Poly Viso recorder Model 154

Results

The alcohol intoxicated animals (Groups I and III) appeared to be very much sedated and lethargic When attempting to crawl up the side of the cage the intoxicated animals would sometimes fall on their backs, and the righting reflex was often sluggish Aside from these observations, the animals appeared to be normal as to hair color and texture and general appearance of mucous membranes around the nose mouth and eyes, and gastric mucosa

Fig 1 shows the intake of fluid of the four groups The intake of fluid of the alcoholic group (I) was about the same as that for the vitamin alcoholic group (III) the intake for both of these groups was somewhat lower than that of the control groups receiving only water The pair fed control group (II) drank less water than *did the normal control group (IV) which* may have been due to the greater intake of food and the more rapid increase in weight of the normal controls. The daily intake of food of the alcoholic group (I) was consistent throughout the study approximately 12 grams per day This also represents the intake of food of Groups II and III since the alcoholic vitamin group (III) and control group (II) were pair fed daily animal for animal with the alcoholic group (I) The intake of food of the normal controls was approximately twice that of the alcoholic group

A graph of comparative animal weights appears in Fig 2 No attempt was made to control the weights of any single group Instead only nutritional food and caloric intakes were controlled The weights of the alcoholic group (I) were consistent with those of the alcoholic vitamin group (III) The vitamin supplement did not

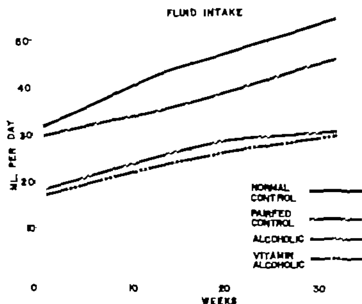


Fig. 1 Graph of the mean intake of fluid of the four groups of animals in milliliters per day. Normal control and pair-fed control animals received only water. Alcoholic and vitamin-alcoholic animals received a 25 per cent solution of ethyl alcohol.

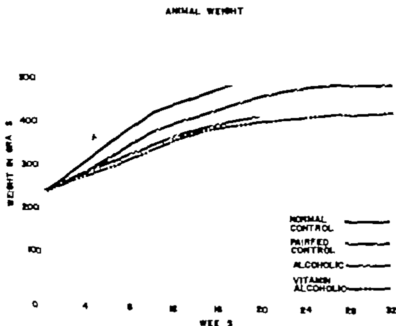


Fig. 2. Comparative animal weights in grams. Normal control and alcoholic group received food ad libitum. The vitamin-alcoholic and pair-fed control animals were pair fed daily with the alcoholic group.

protect the alcoholic animals against a reduced rate of gain in weight. Although all animals gained weight, it can be seen that the weights of both control groups were above those of the alcoholic animals, the normal control showing the most rapid gain in weight.

Figs. 3 and 4 are tracings from typical experiments during the first month which shows developed tension (IST), blood pressure (BP), heart rate (HR), and electrocardiogram (EKG). The developed tension of the control animal in Fig. 3 was about 21 and 22 grams at 8 and 12 grams

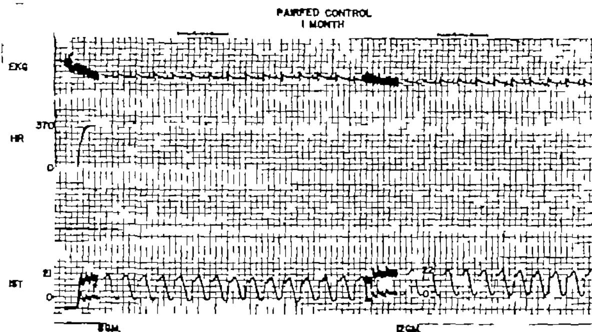


Fig. 3. Record of control experiment during the first month. *EKG*, Electrocardiogram (Lead II). *HR*, Heart rat (beats per mi ute). *IST*, Isometric systolic tension (grams). Recording speed 1 mm. per second and 100 mm. per second. The pplication of 8 and 12 grams of end-diastolic tension to the segment of muscle under measurement is shown.

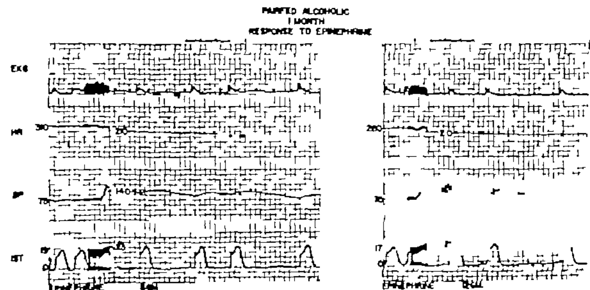


Fig. 4. Record from a 1-month lcohol-intoxicated rat showing the cardiovascular response to epinephrine μg per kilogram intra enously) t 8 nd 12 grams of end-diastolic tension. *EKG*, Electrocardiogram (Lead II). *HR*, Heart r t (beats per minut). *BP*, Carotid arterial blood pressure (mm. Hg). *IST*, Isometric systolic tension (grams). Recording speed 1 mm. per second and 100 mm. per second. Notice the ardiac arrhythmias after epinephrine.

of end-diastolic tension respectively The 1 month alcoholic intoxicated animal (Fig 4) developed 19 grams of tension before epinephrine, typifying the group during the first month which was similar to the control group Two micrograms per kilogram of epinephrine produced a 21 per cent increase in IST which actually reversed to a negative inotropic response in several animals that had been on alcohol for 5 months or longer Epinephrine generally produced a slight to moderate bradycardia during the course of our experiments. This may have been a reflex bradycardia stimulated by the marked hypertension elicited by epinephrine. In addition the epinephrine stress often produced marked cardiac arrhythmias, ectopic ventricular beats, and varying degrees of heart block in animals receiving alcohol

A progressive increment in myocardial tension was observed in control groups (II and IV) throughout the study This is probably related to a gain in weight and increased cardiac function accompanying normal growth There was little change in potential myocardial contraction in the alcoholic groups (I and III) until the sixteenth week when the tension began to fall off rapidly and decrease progressively from a control of 22 grams to 10 grams during the thirty-second week.

Fig 5 shows the general trend of myocardial depression derived from the mean IST values for each week. The blood pressure and heart rate of the alcoholic animals were consistently lower (40 to 50 per cent) than those of the controls. In some instances during the latter stages of the study enlarged dilated alcoholic hearts were observed These hearts could not tolerate mechanical or epinephrine stimulation as shown by a marked tendency toward cardiac arrhythmias.

Fig 6 shows the myocardial depression that occurred after 7 months of alcohol intoxication The alcoholic (Fig 6,*A*) and pair fed vitamin alcoholic animals (Fig 6,*B*) developed less than one half of the IST of the pair fed control animal (Fig 6,*C*) It is apparent that the vitamin supplement did not protect against the cardiotoxicity produced by the administration of ethyl alcohol. The pair fed control animal developed significantly more IST than did the alcoholic and alcoholic vitamin animals, although its nutritional intake was identical except for the substitution of water for alcohol

Discussion

The results tend to support the concept that the chronic consumption of alcohol results in myocardial damage despite

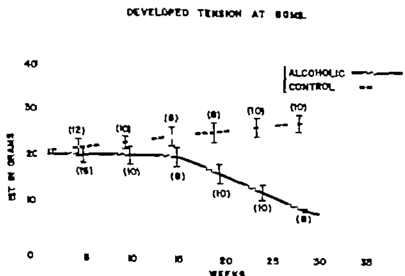


Fig 5 Trend of myocardial depression after ingestion of ethyl alcohol Isometric systolic tension (*IST*) in grams. Graphed lines are drawn through the means of each group. The vertical bars represent the standard error of the mean. The number of animals represented by each of the vertical bars is indicated by the number in parentheses.

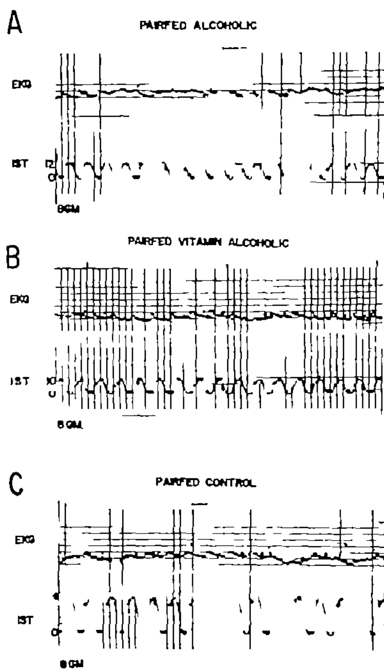


Fig. 6. Effects of ethyl alcohol in the rat after 7 months of oral administration. *EKG*, Electrocardiogram (Lead II). *IST*, Isometric systolic tension (grams). Recording speed: 100 mm. per second. End-diastolic tension 8 grams. Alcohol-intoxicated animal (*A*), pair-fed vitamin-alcoholic animal (*B*), pair-fed control animal (*C*).

adequate intake of food. Nutritional requirements were controlled by the division of the animals into four separate groups in which the intake of food calories, and vitamins was regulated. The consumption of alcohol was determined to be equivalent to the ingestion of approximately 2.5 liters (3 fifths) of 100-proof whiskey per day by a 70-kilogram man. Although this appears to be a large amount, Aull[11] has shown that the rate of metabolism of ethanol in the rat is approximately 270 mg. per kilogram per hour or about twice that in man.

Myocardial depression occurred only in the alcohol intoxicated groups (I and III) although the pair fed control group (II) received equal nutrition. The nutritional intake of the alcoholic groups appeared to be adequate as indicated by the pair fed control Group II maintaining the same myocardial contraction as control Group IV throughout the study. Therefore it is thought that the two times the minimum daily requirement of vitamin supplement administered to Group III was more than sufficient to insure against vitamin deficiency. The fact that this supplement did not protect against myocardial depression and that the pair fed control animals maintained normal cardiac function suggests that the decreased myocardial contractility was not due to nutritional deficiency. Contrary to one current hypothesis, according to which the changes in chronic alcoholism are attributed not directly to the alcohol but rather to the accompanying state of nutrition,[12] the present study indicated that alcohol is elemental in the production of heart disease.

For some time investigators have been interested in the acute toxic effects of alcohol. Gimeno[13] demonstrated the in vitro depression of myocardial contractility of rat atria by ethanol. He noticed that with a dose of 110 to 880 mg. per cent an almost linear relationship existed between the concentration of alcohol and the decline in myocardial contractility. Walam[14] has reported the effects of ethanol on the isolated turtle heart. Low concentrations less than 300 mg. per cent had insignificant effects whereas higher concentrations produced progressive cardiac dilatation, reduction in contractile amplitude, *slowing* of the beat, and occasional arrhythmias. In vivo dog experiments of Loomis[15] showed that high concentrations of ethanol in the blood (880 mg. per cent) produced cardiac depression as indicated by heart rate, blood pressure, and electrocardiographic changes. Haggard and associates found that, in the artificially respired rat, concentrations of ethanol in the blood of 1,300 mg. per cent were required to produce irregular rhythm and cardiac failure, as indicated first by heart sounds; then when the chest was opened the ventricles appeared to be relaxed and the contractions weak. In our present study the acute infusion of 2 ml. of 50 per cent ethanol over a period of 20 minutes to artifically respired control rats resulted in death due to progressive cardiac depression as shown by direct measurement with the strain gauge lever system. These observations suggest that alcohol administered acutely in high concentrations produces a direct toxic effect on the myocardium.

The cardiovascular changes observed during the chronic oral administration of ethanol in this study were manifested by a progressive depression in potential myocardial contraction, accompanied by a decrease in both aortic blood pressure and heart rate, with a marked tendency toward the production of cardiac arrhythmias. Concerning the hypotension produced by the chronic consumption of alcohol, this could be secondary to a decrease in cardiac output concomitant with bradycardia and depression of cardiac contractility. The apparent over-all depression of the sympathetic nervous system may be related to a diminution and depletion of circulating catecholamines, as well as to depression of the central nervous system. If the cardiovascular reflexes are operating normally, an increase in sympathetic activity should accompany cardiovascular depression. In turn, one or more of the parameters mentioned will tend to return toward or above normal in an attempt to compensate for the abnormal cardiovascular function. Anton has shown that a moderate acute dose of ethanol results in an increase in urinary catecholamines in man. This could indicate a release with eventual depletion of certain central and/or peripheral stores of sympathetic chemical mediators. It has been suggested that this alcohol-induced depletion of catecholamines from intracellular sites is analogous to that due to reserpine.[7] Usually catecholamine depletion by reserpine sensitizes the cardiovascular system to epinephrine; however, toward the termination of the present study the epinephrine response progressively decreased and often resulted in a negative inotropic response. This would again indicate that alcohol has a direct toxic action on the heart. Since alcohol is a primary depressant of the central nervous system, cardiovascular

depression may also be partially attributed to a direct reduction in central cardiac and vasomotor activity. These two mechanisms depletion of catecholamines and depression of the central nervous system may therefore contribute to the over-all cardiovascular depression observed in the present study.

Myocardial metabolic alteration in chronic alcoholic patients has recently been demonstrated by several investigators. Ferrans[1] and co-workers histochemically have shown the accumulation of lipid in the myocardial fibers and varying degrees of mitochondrial damage by a decreased staining reaction for several mitochondrial oxidative enzymes. Recent electron microscopy studies by Ferrans[20] and Hibbs,[21] and associates, of the myocardium from patients with alcoholic cardiomyopathy indicated the presence of swelling and rupture of mitochondria alterations of the mitochondrial cristae formation of dense intramitochondrial inclusions, swelling of the endoplasmic reticulum and the deposition of liquid droplets in the myocardial cells. These studies indicate that the mitochondria of cardiac muscle of patients with alcoholic cardiomyopathy are grossly damaged. The present findings are in agreement with these investigations, in that a decrease in the production of energy may be responsible for the myocardial depression observed in our animals on chronic alcohol consumption.

The above mentioned findings are further supported by biochemical changes in the myocardium similar to these histochemical observations demonstrated by the administration of alcohol.[22] In vivo studies by Wendt and associates[23] showed the release of oxidative enzymes from the myocardium of alcoholic patients. Wendt's study suggests that changes in membrane permeability and the liberation of enzymes as a result of alterations of intracellular metabolic pathways exist in the diseased alcoholic myocardium. Ferrans[1] concludes that these observations indicate a process of widespread myocardial degeneration with an end result of cell death and healing by fibrosis. The reduced oxidative enzyme activity and abnormalities demonstrated by the above-mentioned investigators may be largely responsible for the decreased myocardial contractility and increased ventricular automaticity observed in the present study. Although we realize that there may be other unknown metabolic changes, the interpretation of our results lead us to conclude that the chronic ingestion of ethyl alcohol directly contributes to myocardial damage. Nutritional deficiency may be virtually eliminated by means of our method of pair feeding whereby all animals received equal nutritional intake. Sections of myocardium from control and alcohol intoxicated rats in the present study have been preserved for histochemical studies of respiratory enzymatic activity and electron microscopy analysis. We intend to report on these changes in the near future.

In clinical cases in which no overt evidence of malnutrition or vitamin deficiency was seen, several investigators[24, 27] have attributed the production of alcoholic cardiomyopathy to an excessive consumption of alcohol over a long period of time. However malnutrition could not have been definitely excluded in these alcoholic patients. The pathologic effects of the chronic ingestion of alcohol seen in this experimental study support these clinical hypotheses and suggest that alcohol itself is directly instrumental in the production of heart disease.

Summary

Ethyl alcohol (25 per cent) was administered orally to rats over a period of 7 months. After 4 months of alcohol administration a consistent decrease in potential ventricular contractile force (isometric systolic tension), blood pressure and heart rate occurred; however, the pair fed controls remained normal. A vitamin supplement did not protect the alcohol-intoxicated animals against the myocardial depression. Arrhythmias which followed the administration of epinephrine or mechanical stress were noted in the alcoholic group and enlarged dilated hearts were observed in many instances.

The decrease in myocardial tension appears to be the result of alcohol itself rather than nutritional or vitamin deficiencies. Possible mechanisms for the cardiac depression that followed the administration of ethyl alcohol are discussed.

W are indebted to Mrs. Maria G McCarthy B.S.M T (ASCP) for technical assistance and to Mrs. Catherine Teel for services rendered.

REFERENCES

1 Leifer S Jones, D P and Decarli, L. M Effects of prolonged ethanol intake Production of fatty liver despit adequate diets, J Clin Invest. 44 1009 1965
2. Klatskin, G. Alcohol and its relation t liver damage, Gastroenterology 41:443, 1961
3. Walshe, W H Diseases of the heart and great vessels, ed. 4 London, 1876. Cited by Wendt, V E. Hemodynamic and metabolic effects of chronic alcoholism in man, Am J Cardiol. 15 183 1965.
4 Bridgen, W Uncommon myocardial diseases The noncoronary cardiomyopathies, Lancet 2 1179 1243, 1957
5. Burch, G. E., and Walsh, J J Cardiac insuf ficiency in chronic alcoholism, Am. J Cardiol. 6:864 1960
6. Evans, W Alcoholic cardiomyopathy Am. H ART J 61:556, 1961
7 Evans, W Alcoholic myocardiopathy Prog Cardiovas. Dis. 7 151 1964
8. Cotten, M. deV and Maling, H M Relationships among stroke work, contractile force and fiber length during changes in ventricular function, Am. J Physiol. 189:580, 1957
9 Aldinger E. E. Effect of thiamine deficiency on potential myocardial contractility Circulation Res. 16:238, March, 1965
10. Szent-Gyorgyi, A. Chemical physiology of contraction in body and heart muscle, New York, 1953 Academic Press.
11 Aull, J C., J Roberts, W J and Kinard, F W Rate of metabolism of ethanol in the rat, Am. J Physiol. 186:380, 1956
12. Gould, S. E., editor P thology of the heart, ed. 2, Springfield, Ill. 1960, Charles C Thomas.
13 Gimeno, A L Gimeno, M. F and Webb, J C. Effects of ethanol on cellular membrane potentials and contractility of isolated rat atrium, Am. J Physiol. 203 194, 1962.
14 Wakim, K. G. The effects of ethyl alcohol on the isolated heart, Fed. Proc. 5 109 1946.
15 Loomis, T A The effect of alcohol on myocardial and respiratory function Quart. J Stud. Alcohol 13:561 195_
16. Haggard, H W Greenberg L. A., Cohen L. H., and Rakieten, N J Studies on the absorption, distribution and elimination of alcohol. The concentration of alcohol in the blood causing primary cardiac failure, J Phar macol. & Exper Therap. 71:358, 1941
17 A ton A. H Ethanol nd urinary catecholamine in man, Clin. Pharmacol. Therap. 6:162 1965
18. Kalant, H The pharmacology of lcohol intoxication, Quart. J Studies Alcohol, Suppl. 1 1 1963
19 Ferrans, V J Hibbs, R. G Weilbaecher D G., Black, W C., W lsh J J and Burch, G. E. Alcoholic cardiomyopathy AM. HEART J 69 748, June, 1965
20. Ferrans, V J Hibbs R. G nd Weilbaecher D G Alcoholic cardiomyopathy A histochemical nd electron micro-copic stud Am J Cardiol. 13 106 1964
21 Hibbs, R. G., Ferrans, V J Black, W C Weilbaecher D G Walsh, J J and Burch, G. E. Alcoholic cardiomyopathy AM. H ART J 69 776, 1965.
22. Regan, T J Moschos, C B Cassnegra, P Korovonidis, G., and Hellems, H. K. Depression of cardiac function and ltered myocardial metabolism after ethanol, Ann I t. Med. 60 709 1964
23. Wendt, V E., Wu, C. Balcon, R., Doty D and Bing, R. J Hemodynamic and metabolic effects of chronic alcoholism in man, Am. J Cardiol. 15 175 1965
24 Burch, G. E., and Walsh, J J Cardiac insuf ficiency in chronic alcoholism, Am. J Cardiol. 6:864 1960.
25 Elliaser M and Giansiracusa, F The heart and alcohol, California Med. 84:234, 1956.
26. Ferrans, V J Burch G E Walsh, J J and Hibbs, R. G. Alcoholic cardiomyopathy Bull Tulane U iv Med Fac. 24 119 1965
27 Dimas, D E. Alcoholic cardiomyopathy Rocky Mountain M. J 62:32, 1965

Time-normalized correlation of ventricular activation and the vectorcardiogram

*John P. Boineau, M.D.**
Madison S. Spach, M.D.
*Charles R. Ayers, M.D.***
Durham, N. C.

The increasing application of the physical sciences to the field of electrophysiology has emphasized the need for a more precise delineation of the factors which determine the peripheral electrocardiogram. A major impediment to obtaining a universally acceptable method of recording the surface electrocardiogram has been due to the lack of sufficient understanding of the relationship between the curves recorded at the body surface and the characteristics of the heart generator. Burger has indicated the necessity for a rigorous analysis of the electrical process within the heart and its peripheral reflection as changing body surface voltages. Previous work in this laboratory has demonstrated the feasibility of studying this relationship and this report represents a correlation of these internal and external events.

There have been many excellent investigations in regard to the physical basis of the electrocardiogram and vectorcardiogram.[1-4] Some of these have utilized surface voltage data obtained in the presence of artificial simple generators introduced into experimental tanks and torso models[1] into animals,[1] and even in man.[11] Cohen and co-workers[12] have discussed the theoretical relationship between ventricular excitation and the vectorcardiogram. Of particular significance are the reports of Scher,[14,15] Schaefer,[1-17] Durrer,[8-20] Moore,[21] and Sodi Pallares,[22] and their co-investigators, who have studied the normal and abnormal cardiac generator by means of myocardial electrodes. In previous studies of ventricular excitation the data have not been spatially displayed or time normalized specifically for the purpose of relating them to surface events (e.g., the vectorcardiogram). Since the QRS complex at the body surface is the resultant of a specific sequence of excitation in many simultaneously excited myocardial regions, a global model of depolarization is necessary for a realistic correlation. Investigations utilizing complete activation and representative surface data are scant in both normal and abnormal experimental states.[23]

These studies were designed to achieve a more complete definition of the cardiac generator in relationship to the curves recorded from the body surface. By cor

From the Departments of Pediatrics and Medicine, Duke University School of Medicine, Durham, N. C.
Supported in part by United States Public Health Service Grants HE-3349 and HTS-5275 and a grant from the North Carolina Medical Research Fund.
Received for publication March 7, 1966.
*Postdoctoral Fellow of the National Heart Institute, National Institutes of Health.
**Work done during a Student Fellowship sponsored by the Hanes Fund, Duke University School of Medicine.

relating the activation process with the vectorcardiogram in the normal dog then inducing a change in the process of excitation (e.g. right bundle branch block) and again observing the internal and external correlation, a more complete understanding of the vectorcardiogram in terms of the heart's activity is achieved

Methods

Vectorcardiographic methods Vectorcardiograms were recorded in 31 dogs, weighing 15 to 22 kilograms, utilizing the equilateral tetrahedron reference system with a Sanborn 185 Vector Amplifier and Viso-scope. The beam was interrupted at 0 0025 second for timing purposes. Additionally recorded were the scalar tracings of X Y and Z axes. Q R, and S components of the vectorcardiograms were identified according to the method of McCall and co-workers.[24] Their spatial coordinates were determined from the X Y and Z scalar tracings. The spatial magnitudes for each vector (E) were calculated from the formula

$$E = \sqrt{Ex^2 + Ey^2 + Ez^2}$$

After the original tracings were obtained the animals were divided into three groups. Group 1 was comprised of 10 dogs in which no surgery was performed and repeat tracings were obtained 6 weeks after the initial recording Group 2 was comprised of 10 dogs which were subjected to right thoracotomy and pericardiotomy after which the chest was closed. These two groups served as controls to determine the consistency of the vectorcardiogram in dogs when recorded at different times and to determine if thoracotomy altered the vectorcardiogram Group 3 consisted of 11 dogs which were subjected to thoracotomy and the production of right bundle branch block according to the method of Erickson and co-workers.[25] The electrocardiogram was monitored throughout the operation and after section of the right bundle the QRS duration was prolonged to 0 067-0 075 second In Groups 2 and 3 repeat vectorcardiograms were obtained 6 weeks after surgery

Ventricular activation Ventricular activation studies were performed in 20 control dogs and in 11 animals with right bundle branch block. Scher multipolar myocardial electrodes were utilized[26] and 20 to 25 electrodes were inserted into each heart. Each electrode consists of 15 fine, insulated tungsten wires assembled around a central shaft. The uninsulated tips are approximately 1 mm apart with the maximum diameter of the entire assembly being 0.3 mm The electrodes are connected to a recording ensemble consisting of twelve Type 122 Tektronix preamplifiers in a series with Honeywell power amplifiers which drive miniature fluid-damped galvanometers of a 12-channel Visicorder oscillograph The frequency response of the recording system is flat to 1 000 cycles per second. All records were obtained at a paper speed of 500 mm per second Throughout each experiment Lead II of the electrocardiogram was monitored on Channel 12 and a fixed time reference bipolar lead in the left ventricle was recorded on Channel 11

Each dog was anesthetized with intraperitoneal pentobarbital Artificial respiration was administered via an endotracheal tube. The chest was opened with a longitudinal sternum-splitting incision and the heart was cradled in the pericardium Initially electrodes were placed in the free walls of both ventricles and then advanced into the septum and crista supraventricularis. The configuration of the Lead II electrocardiogram was carefully monitored to determine that no change occurred throughout the study At the conclusion of each experiment the electrodes were passed through the heart and a fine thread was attached to each electrode and withdrawn through the heart for permanent identification of electrode tracts. Approximately 9 000 measurements from 425 insertions formed the basis of the activation study

Correlation of the sequence of ventricular activation with the vectorcardiogram was performed in the following manner (1) Local activation times of specific myocardial areas were measured with respect to the peak of the R wave in Lead II (Channel 12) (2) The peak of the R wave in the electrocardiogram was related to the R component in the X lead of the vectorcardiographic scalar tracing (3) Isochronous time-distance periods (isochronous

surfaces) were determined to correspond with time chosen from vectorcardiographic loops as indicating a significant period of or a major change in electrogenesis. When the isochronous maps are so constructed for frozen periods in the sequence of excitation, their outer borders correspond to the instantaneous distribution and geometric balance of dipole layers (double layer or doublet). The area between the outer and inner boundaries indicates the direction of movement of the doublets and approximates the mass of the myocardium depolarizing during the interval (Figs. 2 and 3).

Results

I. Vectorcardiography. Table I presents the quantitative data of spatial voltage of the Q, R, and S components for the two periods of recording in the three groups of dogs. Groups 1 and 2, the nonsurgical and surgical controls, demonstrated no significant change in spatial voltage of the Q, R, and S components. The animals with surgically produced right bundle branch block (Group 3) manifested significant changes in all three loop components (Q, R, and S). There was a marked increase in the spatial magnitude of the S component in all dogs in the latter group. Also, there was a conspicuous decrease in the spatial magnitude of the R component subsequent to the right bundle branch block. The spatial magnitude of the postoperative R loop amounted to less than one half of its original control value. In addition, there was a significant decrease

Table IA. Effect of RBBB on the spatial voltage of Q, R, and S

Group	Number of animals	Component	Period 1		Period 2		p Value
			Mean (mv)	S.D.	Mean (mv)	S.D.	
		Q	0.27	0.13	0.28	0.16	99%
1	10	R	1.10	0.34	1.10	0.30	99%
		S	0.01	0.01	0.02	0.01	99%
		Q	0.24	0.11	0.19	0.03	99%
2	10	R	1.01	0.25	0.96	0.50	99%
		S	0.20	0.14	0.20	0.18	99%
		Q	0.34	0.17	0.14	0.03	<0.01
3	11	R	0.80	0.17	0.32	0.11	<0.001
		S	0.07	0.05	0.70	0.17	<0.001

The spatial voltage, in millivolts, of Q, R, and S components of the loop are indicated for the nonsurgical controls (1), the surgical controls (2), and the group in which right bundle branch block was produced (3). Period 1 represents the initial values for the three groups. Period 2 indicates the values 6 weeks postoperatively in Groups 2 and 3; Group 1 did not undergo surgery and the two periods were compared to determine the consistency of results at 6-week intervals.

Table IB. Effect of RBBB on the spatial voltage of Q, R, and S

Component	All control		RBBB		p Value
	Mean (mv)	S.D.	Mean (mv)	S.D.	
Q	0.28	0.15	0.14	0.03	<0.01
R	0.94	0.32	0.32	0.11	<0.001
S	0.10	0.05	0.70	0.17	<0.001

The mean values of Q, R, and S for all of the non-right bundle branch block loops preoperatively and postoperatively were compared with the post-right bundle branch block loops. See text for discussion.

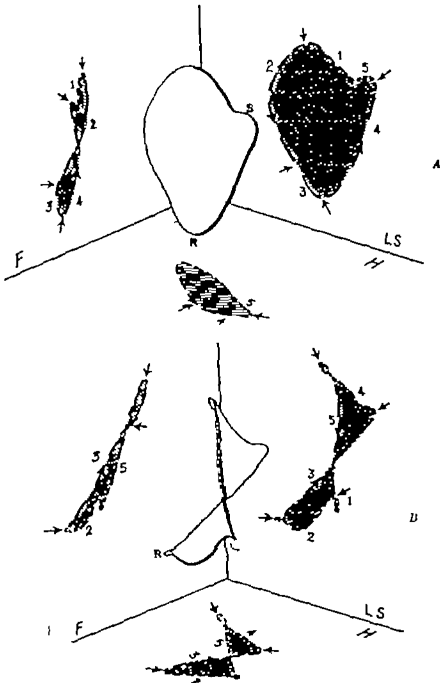


Fig. 1. The composite vectorcardiogram of the normal dog (A) and after complete right bundle branch block (*B*). The three-dimensional vectorcardiogram is illustrated along with its spatial projection onto three planes of the coordinate reference system. The loop is viewed from a left lateral and posterior aspect. *F* = frontal plane (viewed from back to front); *LS* = left sagittal; and *H* = horizontal. The spatial characteristics of displacement, orientation and symmetry of the loop are demonstrated by the composite vectorcardiogram. The parameters of sense of rotation and velocity are indicated in the projected loops and may be appreciated spatially from their relationships to the composite tracing. The loops are divided into five segments (1-5) and each segment is denoted between two arrows. Segment 1 is between the central dot and the first arrow. Note that the plane of the normal QRS loop lies almost parallel to the left sagittal vectorcardiogram. Also, compare the spatial parameters of displacement (magnitude and orientation) of Q, R, and S components as well as velocity, rotation, and the degree of planar symmetry of the normal and right bundle branch.

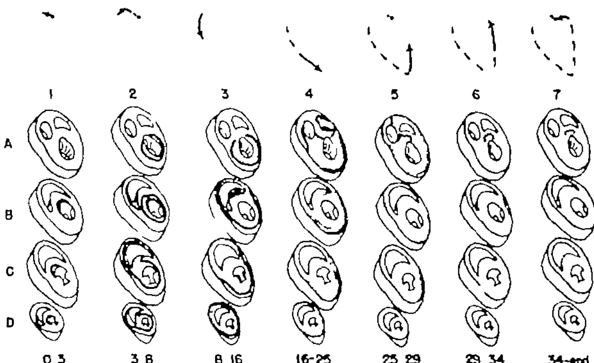


Fig. 2. The normal dog. Correlation of the sequence of ventricular excitation with the vectorcardiogram. Depolarization is depicted in four sections of the heart from base to apex (A-D) and is divided into seven periods (1-7). The time in milliseconds is indicated below each period. The volume of muscle to undergo excitation during the intervals is represented by the stippled area. The dark border of the stippled area indicates the instantaneous distribution of the dipole layer(s) at the conclusion of each time interval, and the inner border of the stippled area denotes the dipole layer at the onset of each interval. The left broad side view of the vectorcardiogram is presented for the correlation. The direction of inscription of the vectorcardiogram is indicated by the arrow. The tip of the arrow corresponds in time to the instantaneous position of the dipole layer in the four sections (the dark outer boundary of excitation). The beginning of the solid vector in the accompanying loops corresponds in time to the inner boundary of the stippled area. The time normalization of the events of excitation with the vectorcardiogram demonstrates the effect of the former on the latter.

in the spatial voltage of the Q component in this group.*

Fig. 1,A and B illustrates the projection of the spatial QRS loop onto the three coordinate planes of the reference system in the normal dogs and in those with right bundle branch block, respectively. The vectorcardiographic parameters of spatial voltage, orientation, velocity, and sense of rotation for each of the three planes can be appreciated from inspection of the spatial loop and its relationship to the reference system. It should be noted that the frontal plane vectorcardiogram is viewed in reverse (back-to-front) in these projections.

*In view of the limitations of the reference systems, the degree of difference in vectorcardiographic parameters in the control and RBBB animals cannot be interpreted as representing absolutely comparable quantitative changes in excitation.

A. THE NORMAL VECTORCARDIOGRAM. The spatial QRS loop of the normal dog tends to approximate a plane (Fig. 1,A). Deviations from this plane are indicated by the figure-of-eight configuration of the frontal plane projection. The plane of the loop is nearly parallel to the left sagittal plane of the reference system and is edgewise to the frontal plane. The rotation of the spatial loop is counterclockwise when viewed from its left side. The initial limb of the spatial loop moves superiorly, anteriorly, and slightly to the right at a moderate spatial velocity. At the point defined by the Q it angulates and proceeds inferiorly to the left at a more rapid spatial velocity. At the point of its maximal inferior displacement, as defined by R, it again changes direction and progresses superiorly and posteriorly at its most

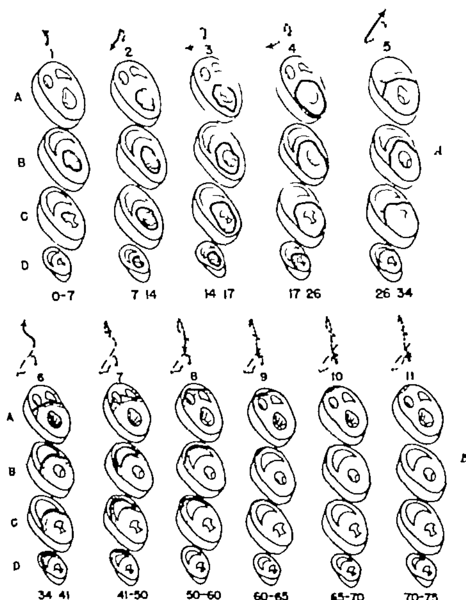


Fig 3 A and B Correlation of the sequence of ventricular excitation with the vectorcardiogram in right bundle branch block Depolarization is divided into eleven periods. The four sections of the heart the areas undergoing excitation and vectorcardiogram are presented as in Fig 2.

rapid spatial velocity to the position defined by S. From the peak of S it moves at a slow spatial velocity anteriorly toward the isoelectric point.

B THE VECTORCARDIOGRAM IN RIGHT BUNDLE BRANCH BLOCK. A description of the vectorcardiogram of right bundle branch block in the dog is best presented as a comparison with the normal vector cardiogram. Note that only the small inferior anterior portion of the loop approximates the normal plane (Fig 1,*B*) The remaining superiorly oriented portion of the loop is twisted and deviates from the original plane There is a marked diminution in the spatial magnitude of the Q loop (Segment 1) as the initial limb projects superiorly and somewhat anteriorly then proceeds inferiorly and anteriorly to the left at a relatively slow spatial velocity (Segment 2) Upon reaching the point defined by R, the loop turns

and progresses at a rapid spatial velocity superiorly and to the right (Segment 3). From this location, it again angulates and proceeds at a much slower spatial velocity anteriorly, superiorly, and to the right (Segment 4) to the point defined by S. From the summit of maximum superior displacement, it turns acutely and proceeds at a slow spatial velocity (Segment 5) toward the isoelectric point.

The diminished Q and R voltages and the increase in the magnitude of the S are graphically illustrated by comparing *A* and *B* of Fig. 1. Note that in right bundle branch block the spatial velocity is slow initially and terminally, with only one rapid segment interposed between these two phases. There was marked departure from the characteristic symmetry and displacement of the normal loop. However, these changes subsequent to right bundle branch block were consistent in all animals. This was true for all major angulations, as well as for the notching which was present in Segment 4 (Fig. 1 *B*).

II. Correlation of ventricular activation with the vectorcardiogram. Fig. 2 illustrates the sequence of excitation related to the vectorcardiogram in one normal dog. The transmural components of excitation are presented in four sections from base to apex, the plane of each section is approximately parallel to the base of the heart. Ventricular activation time is presented from left-to-right, and the depicted intervals represent the excitation process during corresponding vectorcardiographic intervals. These are indicated for each time period above the individual heart sections. The orientation of the four sections relates the position of the heart to the left broadside view of the spatial loop. In order to use this view of the spatial vectorcardiogram, it was necessary to visualize the heart in its approximate spatial position relative to this plane. The broad, open surface of the three-dimensional loop (i.e., the plane of the loop) is more easily correlated with the process of excitation than other spatial views.

The dipole layer is indicated by the heavy outer boundary in each of the four sections. The position of this dipole layer in each section coincides in time with the point of the vector in the accompanying vectorcardiogram. The stippled area corresponds to the mass of myocardium to undergo depolarization during the interval encompassed by the solid segment of the associated vectorcardiogram. The projections of the spatial vectorcardiogram onto its three coordinate planes in Fig. 1,*A* and *B* may also be used to arrive at a three-dimensional perspective of the correlation. The following description of activation and the vectorcardiogram in both a normal dog and an animal with right bundle branch block are representative examples of the two groups.

A. NORMAL VENTRICULAR EXCITATION AND THE VECTORCARDIOGRAM (FIG. 2)

(1) *0-3 Milliseconds.* Activity is present in the left septum and can be noted to move upward (left to right in the septum), forward, and rightward. There is also activity in the right free wall which spreads outward. The vectorcardiogram moves superiorly, anteriorly,* and to the right.

(2) *3-8 Milliseconds.* Note the circumferential surface or "cone" of activity surrounding the left ventricular cavity which is closed ventrally and open dorsally. There is also a broad zone of depolarization in the right free wall. The resultant effect of this electromotive distribution causes anterior vectorcardiographic displacement.

(3) *8-16 Milliseconds.* The ventricular septum is depolarized first at its ventral aspect by double envelopment of activity progressing from both left and right endocardial surfaces (see *3-8 milliseconds*). Subsequently, the remaining two thirds of the septum are activated from left to right (caudal to cranial and ventral to dorsal). Coincident with waning excitation of the septal mass in sections *B* through *D*, the vectorcardiogram rotates inferiorly because of the dominant influence of the uncancelled wave front in the left ventricular free wall.

(4) *16-25 Milliseconds.* As excitation proceeds dorsally toward the base of the left ventricle, the loop swings posteriorly.

(5) *25-29 Milliseconds.* Waning activity is present in the dorsal and basal left ventricle and depolarization of the basal

*Anterior, posterior, superior, and inferior denote vectorcardiographic displacement in space. The terms *ventral, dorsal, cranial,* and *caudal* represent the respective anatomic positions in the dog.

right ventricle is also shown. The vector cardiogram continues posteriorly since these areas are dorsal to the electrical center of the heart.

(6) 29-34 Milliseconds Excitation of the outflow tract of the right ventricle and crista supraventricularis is completed during this period only activity in the basal left ventricle and high central septum remains. The vectorcardiogram continues its inferior counterclockwise inscription.

(7) 34 Milliseconds to Completion In this dog the latest area of activation was noted in the high septum adjacent to the aortic annulus. Terminally the loop moves with a slow spatial velocity back to the isoelectric point.

B VENTRICULAR EXCITATION AND THE VECTORCARDIOGRAM IN RIGHT BUNDLE BRANCH BLOCK. Fig 3 illustrates the sequence of ventricular activation in the dog with right bundle branch block. The left view of the spatial loop is presented for the vectorcardiographic correlation

(1) 0-7 Milliseconds Excitation begins normally spreading from the left septal endocardium upward (left to right) in the septum. There is concomitant superior displacement in the vectorcardiogram

(2) 7 14 Milliseconds The elongated cone of activity almost encircles the left ventricular cavity and there is no right septal or free wall activity at this time The vectorcardiogram swings inferiorly without the usual degree of anterior displacement noted in normal dogs.

(3) 14-17 Milliseconds The absence of activity on the right side is even more obvious during this period and the conical surface of left ventricular activity moves centrifugally from the endocardium outward The vectorcardiogram continues its slow inferior anterior displacement.

(4) 17 26 Milliseconds The resultant forces which effect the continued slow inferior-anterior vectorcardiographic displacement are due to the highly cancelling cone of activity open dorsally with an "unchanging" centroid of activation directed opposite this opening

(5) 26-34 Milliseconds There is termination of a large portion of left free wall activity with an abrupt superior shift in the centroid of activation due to the relatively unopposed activity in the septum at this time As a result of this sudden shift of the centroid of activity the vectorcardiogram swings superiorly at a rapid spatial velocity

(6) 34-41 Milliseconds There is progressive unopposed left-to-right (caudal to cranial) septal depolarization and the vectorcardiogram reaches its maximum spatial magnitude during this interval During this period of localized septal activity the superior vectorcardiographic displacement proceeds at a relatively slow spatial velocity The undulations observed in the vectorcardiogram which are indicated by Segment 4 of the QRS loop in Fig 1,B relate to a change in the mean direction of the centroid of activation

(7) 41 75 Milliseconds Subsequent wave fronts of activity in the right free wall progressing into the outflow region decrease in surface area and there is decreasing spatial magnitude. The slow spatial velocity in the vectorcardiogram beginning at 34 milliseconds and continuing to the end of the excitation cycle is due to relatively small shifts in the centroid of activity In all of the dogs the maximum spatial voltage was associated with septal activation and not activation of the right free wall

Discussion

I Effect of right bundle branch block on QRS loop Although it is well recognized that marked changes in the spatial magnitude of the terminal vectorcardiographic forces occur after experimental right bundle branch block changes in the Q and R components have received limited attention.[17, 19] These studies confirm the finding of Gould and co-workers[20] that right bundle branch block alters the early portion of the QRS Furthermore they demonstrate a significant change in the magnitude of the Q loop due to absence of early depolarization of the trabecular region of the right ventricular free wall during the first milliseconds. In addition, there was a reduction in the spatial magnitude of the R loop as suggested by Sodi Pallares.[21] Ventricular activation studies show that in the normal heart the maximum spatial voltage (R loop) is the result of the large area of unopposed activity in the left ven

tricle however in right bundle branch block the R loop was related to a highly cancelling cone of activity surrounding the cavity of the left ventricle The maximum spatial voltage in right bundle branch block was related to activation of the ventricular septum The septal dipole layer contributing to the large spatial magnitude of the S loop was *unopposed by other* forces in the previously depolarized left ventricular free wall

The abrupt decrease in the spatial voltage in the electrocardiogram subsequent to its maximum superior displacement begins at a *period when the major* portion of the excitation wave moves from the septum into the right ventricular free wall Except for the time of onset depolarization of the right free wall in right bundle branch block is similar to that in the normal animal The dipole layer first intersects the wall at its low ventral septal junction and continues toward the inflow and outflow regions of the right ventricle in a sequence not unlike that noted in the normal heart However its total excitation time is longer The surface area of the dipole layer in the right free wall is less than the area of the wave during septal activation in right bundle branch block and is associated with decreasing spatial voltage as the vectorcardiogram returns to the isoelectric point at a very slow spatial velocity

The vectorcardiographic angulations and electrocardiographic notching present during the interval of unopposed left-to-right septal activation appeared to be due to shifts in the resultant centroid of activation caused by changes in uniformity of the localized wave of depolarization. Since the centroid of activity is no longer the resultant of many dispersed areas of excitation it is altered by minimal changes in the distribution of the localized activity as it moves across the septum and into the right free wall

II Activation and the parameters of the vectorcardiogram After the activation vectorcardiographic relationships have been observed it is possible to explain several key vectorcardiographic parameters in terms of (1) the excitation process and (2) the geometric relationships between the cardiac generator and the torso points at which potentials are recorded

The parameters of spatial magnitude spatial orientation spatial velocity sense of rotation and the tendency for the voltage displacements to take place in a spatial plane are the result of the dynamic interaction cancellation and final resolution of activation fronts in the heart. Fig 4,*A* indicates the sequence and distribution of *excitation at the ventral epicardium B* and *C* of Fig 4 are sections through the heart and indicate the transmural sequence and distribution of depolarization. The influence of the spatial sequence of excitation *upon* the parameters of the vector *cardiogram can be demonstrated by comparing* the frontal left sagittal and superior plane loops with the pattern of activation and the orientation of the heart in Fig 4,*A B* and *C* respectively Figs. 1 through 3 should also be consulted for the following discussion

A SPATIAL MAGNITUDE. Spatial magnitude of the vectorcardiogram is dependent both on the intrinsic factors of excitation and on certain extrinsic factors (conductivity geometry lead structure etc.) Relevant to the activation process is the degree to which unbalancing of the dipole layer distribution favors one ventricle or the other This unbalancing may result from two mechanisms (1) the greater surface area of a dipole layer in one area causing that structure to dominate a specific interval of depolarization even if more than one region is activated simultaneously and (2) phase difference in excitation due to a specific area undergoing excitation in the presence of very little activity in other opposing areas of the heart (e.g right bundle branch block)

In the normal dog with the usual degree of asymmetry (thickness) favoring the left ventricle the magnitudes of the vectorcardiographic displacements are determined as follows

(1) The magnitude of the initial superior displacement in the vectorcardiogram is a function of the surface areas of the activity originating in the left septum and right free wall. That the excitation of the trabecular region of the right ventricle is important in the magnitude of the initial superior anterior vectorcardiographic forces is demonstrated by the decrease in these forces subsequent to right bundle *branch block with absence of right free*

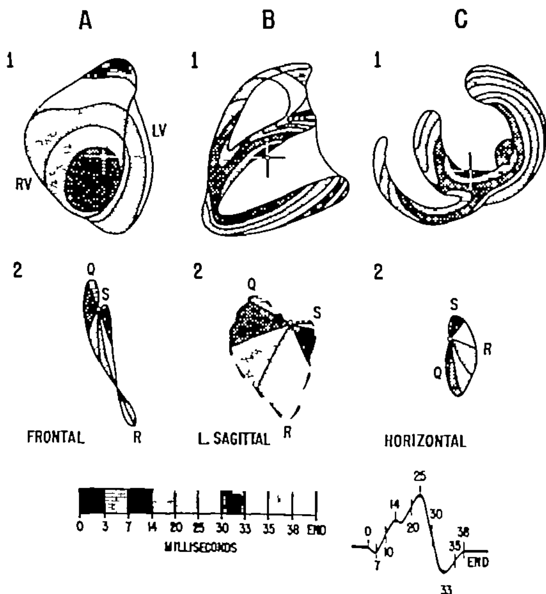


Fig. 4. Ventricular activation and parameters of the ectorcardiogram in the normal dog. A time scale corresponding to the periods hosen from representative electrocardiogram is presented below. Epicardial entric ular excitation is illustrated over the entral aspect of the dog heart in 1 1 and transmural excita ion bout the plane of electrical symmetry of the heart in B-1 and also through an pproximat transverse plane of the heart (C 1 The corresponding frontal (A-2), left sagittal (B-2), nd horizontal (C 2) ectorcardiogram are presented The ectorcardiographic parameters of displacement, otation, and locity can be correla ed w h entricula activation by relating the i tervals of each of the QRS loops with their respectiv interv ls of excitation depicted abov (A 1 B-1 C 1).

wall activity during this period (5-8 milli seconds)

(2) The maximum anterior displace ment in the loop between 10 and 15 milli seconds is principally the result of the large circumferential cone of activity surrounding the left ventricular cavity closed at the apex and open at the inflow region

(3) The point of maximum nferior displacement at 22 25 millisecond is associ ated with the excitation of th left ven tricular free wall subsequent to the term nation of signific ntly opposing forces in the lower two thirds of the nterventricular septum and the right free wall.

(4) The maximum posterior vectorcar diographic displacement at 33-35 m lli-

seconds results from the dorsal activity in the basal (inflow) region of the ventricles. The presence of any terminal superior displacement is presumably the result of activity in regions of the heart superior to the isoelectric center, such as the high central septum, which depolarizes terminally. Since the excitation fronts in these areas are quite small, there is usually negligible terminal superior displacement.

B. SPATIAL ORIENTATION. The spatial orientation of QRS displacement is not only the result of the sequence and distribution of the dipole layers during activation but, as indicated in Fig. 4, is also a function of the relationship between the heart's position and the surface leads. Because of the presence of marked cancellation and resolution of the forces of activation, the relationship between the vectorcardiogram and the heart's position is largely obscured. This association can be appreciated best early in excitation prior to the complex interaction of simultaneous areas of activity, as well as when certain major heart structures tend to dominate activation (Figs. 2, 3,*B*, and 4). The relative position of the heart's major component structures and their relationship to one another (i.e., LV free wall, septum, RV free wall) are especially significant in determining spatial orientation.

Finally, the spatial orientation is influenced by factors extrinsic to the process of excitation and the heart's position. The report of Horan and co-workers[22] emphasizes the importance of the inhomogeneous volume conductor in determining the spatial orientation of vectorcardiographic displacement.

C. SPATIAL VELOCITY. Changes in spatial velocity are the result of variations in the rate of movement of the center of gravity or centroid of activation as it shifts from one area of the heart to another. Figs. 2, 3,*A*, *B*, and 4,*B* show that the rate of change of the centroid can be interrelated with the spatial velocity of the vectorcardiogram. A slow spatial velocity indicates that the center of gravity of excitation is determined by a focal, frequently solitary region of excitation moving in a uniform direction. A segment of rapid spatial velocity indicates a sudden shift of the centroid over a considerable distance between widely separated regions of excitation which are competing for dominance. When two or more major myocardial masses are excited with a difference in their phase of activity, the spatial velocity changes rapidly as the dominance of one area wanes in the face of the emerging dominance of the other.

The initial segment of rapid spatial velocity illustrated in Fig. 4, from the peak of the Q to the peak of R, is associated with the waning influence of the forces in the septum, ventral right and left ventricle, and the rapidly emerging dominance of the forces contributed by the free wall of the left ventricle. The second rapid segment of the vectorcardiogram, corresponding to the intrinsicoid deflection in the scalar electrocardiogram and from R to the peak of S in the figure, begins coincident with the termination of a major portion of activity in the parietal wall of the left ventricle.

If the activation process is altered by right bundle branch block, there are characteristic changes in the spatial velocity which reflect the altered sequence of excitation. In Fig. 3,*A* and *B*, the spatial velocity is correlated with the activation. In the vectorcardiogram after right bundle branch block, there are four areas of changing spatial velocity. Initially, the velocity is slow because of a focal area of unopposed left-to-right (caudal to cranial) septal activation. The velocity increases moderately because of a slight shift of the center of gravity of excitation from the septum to a position determined by the highly cancelling cone of activity in the left ventricle. At this point the only segment of rapid spatial velocity occurs, as excitation terminates in the free wall of the left ventricle and the centroid suddenly shifts upward because of the effect of unopposed activity in the central septum. The subsequent velocity is slow as the relatively localized wave of activation progresses at a rather uniform rate across the septum and into the free wall of the right ventricle.

The appreciation of the mechanism and significance of a change in the rate of spatial velocity is essential for proper vectorelectrocardiographic interpretation. Slowing of terminal vectorcardiographic

inscription does not necessarily indicate a conduction delay or "block"; rather it indicates that the *center of gravity* of activation is moving at a constant rate in a discrete myocardial area and is relatively unopposed by other simultaneously activating areas. Bundle branch block results in unopposed excitation with a constant rate of movement of a localized centroid of activation but there are other mechanisms in addition to Purkinje block which result in the slowing of spatial velocity.[23] Hellerstein and Hamlin[23] originally proposed that variations in the spatial velocity of the vectorcardiogram reflect the rate and degree of change in the location of excitation dominance. The results of the present study are in agreement with their work and indicate that the spatial velocity is not a measure of the speed of ventricular activation. Furthermore it is the result of relatively stationary or rapidly changing centroids of activation whose location rate and extent of change are determined by the shifting balance between dipole layers within the heart.

D. SENSE OF ROTATION. The QRS loop of the normal dog tends to approximate a spatial plane. The orientation of this plane within the dog is independent of the reference system and is determined by the orientation of the heart within the body and the specific nature and sequence of the depolarization process. The frontal, sagittal and horizontal vectorcardiogram can be thought of as projections of the spatial loop onto the three orthogonal planes. Burger and Vaane[24] described the plane of this spatially oriented loop by referring to a vector which is perpendicular to the plane (polar vector) pointing outward from the electrical center of the loop with the rotation of this loop counterclockwise when the plane is viewed from its left side. If the plane of the loop is viewed directly from the side it is maximally open. When viewed from the front at 90 degrees from its plane the loop will appear to be either thin or a figure of eight. In practice the plane of the loop seldom lies exactly in one of the planes of a vectorcardiographic reference system but is intermediate between them. In the dog the plane of the loop is nearly parallel to the sagittal plane. For this reason the loop is widely open in the sagittal plane of the vectorcardiogram and normally is always counterclockwise when viewed in the left sagittal projection (Fig. 4). When the loop is correlated with ventricular activation it can be appreciated that the ventrally directed forces of depolarization cause the vectorcardiogram to be displaced anteriorly initially. As the loop continues inferiorly it remains anterior to the isoelectric point because the forces ventral to the electrical center of the heart dominate this phase. When the vectorcardiogram swings upward it takes a posterior arc because of dominant activity dorsal to the electrical center of depolarization. The sense of rotation in the frontal and transverse projections is determined by the degree to which the loop approximates a plane, and the position of this plane relative to the other lead axes.

Counterclockwise inscription of the spatial QRS loop when viewed from its left side is due to the resultant doublet balance giving rise to a centroid of activation, the instantaneous position of which is determined by dominance of specific myocardial locations whose excitation occurs in a counterclockwise sequence in relation to the electrical center of the heart (i.e., the central septum). This explanation for the sense of rotation of the vectorcardiogram is true for any projection onto a reference system if the relationship of the *heart to the system and the process of* ventricular activation of the heart are known.

E. THE PLANE AND SYMMETRY OF THE QRS LOOP. A significant example of activation *symmetry* is the mechanism associated with the tendency of the QRS loop to lie within a plane. The planar characteristics of the QRS loop have been previously described by Burger,[24] Shellong,[25] and Rijlant,[26] who has postulated a high degree of internal symmetry of excitation to explain this phenomenon. Horan and coworkers,[27,28] in their studies on factor analysis of the electrocardiogram identified eight principal factors of the QRS complex. They suggested that the first two factors (I and II) represent the first order or "dipolar" components of the heart generator and form the QRS plane

These authors also proposed that the remaining six factors represent the nondipolar components of activation and cause the deviations from this plane

From the activation vectorcardiographic correlations presented here it is suggested that the principal factors 1 and 2 describe the sequence of symmetrical activation of the dog's heart When several key instants of excitation are simultaneously viewed in a plane parallel to the heart's base a high order of electrical symmetry is noted (Fig 3) This figure illustrates that the plane of the QRS loop results from mirror image cancellation of forces due to the predominance of activity symmetrically disposed about an electrical axis There is displacement within the QRS plane due to resolution of forces resulting from unbalanced activation oriented along the axis The deviations from the plane of the loop are due in part to activation of myocardial areas which have no balancing counterpart about the major axis of electrical symmetry

Summary

Vectorcardiograms were correlated with ventricular depolarization in normal dogs and after right bundle branch block. Subsequent to right bundle branch block there were changes in spatial voltage of the three major components of the QRS loop There was a decrease in Q-loop magnitude due to the absence of ventral right ventricular free wall activation during the first 7 milliseconds. There was also a decrease in the R loop magnitude due to a persistent circumferential surface of activity surrounding the left ventricular cavity caused by delayed activation of the ventricular septum The increased spatial magnitude of the S component was the result of unopposed left to-right depolarization of the septum Activation of most of the right free wall was associated with decreasing spatial voltage.

The correlation between the heart's depolarization and the curves recorded from the body surface in the two experimental states (i.e. normal and right bundle branch block) provided a model which described the vectorcardiogram chiefly as a function of ventricular activation Five physical parameters of the vectorcardiogram (e.g spatial magnitude spatial orientation spatial velocity sense of rotation and the symmetry and planar characteristics of the loop) were related to the distribution and change of instantaneous electromotive surfaces within the heart

We wish to express our gratitude to Drs. D Durrer H C Burger D A. Brody L. G Horan and B Taccardi and M R C Barr who reviewed the manuscript Also we should like to thank M O R Lipscomb J M Vernon Ross and M Donald Marger for their valuable technical assist

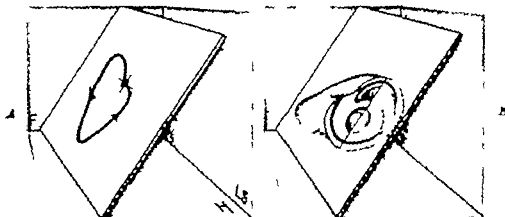


Fig 3 The QRS plane The plane of the QRS loop is presented in A (F = frontal LS = left sagittal H = horizontal) as viewed from the left and posterior Also the position of the heart within the reference system and the spatial distribution of several key instants of ventricular activation (each indicated by dark boundary) about the axis of electrical symmetry are illustrated in B The symmetrical component of excitation form the QRS plane because of (1) cancellation outside the plane and (2) resolution and displacement within the plane

ance during the course of this tudy W are also indebted to M Otis Brow for construction of the Scher electrodes.

REFFRENCES

1 Burger H. C., van Brummelen, A. G. W nd van Herpen, G.: Heart vector and leads, Am. Heart J 61:317 1961
2 Burger H. C. *Personal communication.*
3 Einthoven, W Fahr G., nd de Waart A. Über die Richtung nd die manifeste Grosse der Potential Schwankungen im menschlichen Herzen and über den Einfluss der Herzlage auf die Form des Electrokardiogramms, Pflüger Arch. ges. Physiol. 150:275 1913
4 Lewis, T.. Mechanism and graphic registration of the heart beat, ed. 3 Chicago, 1924 Chicago Medical Book Company
5 Wilson, F W Macleod, A. G nd Barker P S. The distribution of the currents of action and of injury displayed by heart muscle and other excitable tissues, Ann Arbor 1933 University of Michigan Press.
6 Burger H. C., and van Milaan, J B. Heart vector and leads, Brit. Heart J (Part I) 8 157 1946 (Part II) 9 154 1947 (Part III) 10:229 1948.
7 Gelertner H. L., and Swihart, J C. A mathematical-physical model of the genesis of the electrocardiogram, Biophysics J 4:285 1964
8 Selvester R. H., Collier C. R and Pearson, R. B. Analog computer model of the vector cardiogram, Circulation 31:45 1965
9 Gabor D and Nelson, C. V Determination of the resultant dipole of the heart from measurements on the body surface, J Appl. Physiol. 25:413, 1954
10 Frank, E. Absolute quantitative comparison of instantaneous QRS equipotentials on a normal subject with dipole potentials on a homogeneous torso model, Circulation Res. 3:243, 1955.
11 Horan, L. G Flowers, N C and Brody D A Body surface potential distribution, Circulation Res. 13:373 1963
12 Buttersworth, J S., and Thorpe J J On evaluating the Einthoven triangle theory Circulation 3:921, 1951
13 Cohen, W., Abildskov J A. and Jacobson, E. D.. Theoretical and clinical studies of the electrocardiogram and vectorcardiogram in right ventricular enlargement, Am. Heart J 61:656, 1961
14 Scher A. M and Young A C The pathway of ventricular depolarization in the dog, Circulation Res. 4:461, 1956.
15 Scher A. M., and Young A. C. Ventricular depolarization and the genesis of QRS (edited by Hecht) Ann. New York Acad Sc. 65 768, 1957
16 Schaefer H., and Trautwein W.: Über die elementaren electrischen Prozesse in Herzmuskel and ihre für eine Neue Theorie der Electrokardiogramm, Pflügers Arch. ges Ph iol. 251:417 1949
17 Schaefer H. Über die absolute Grosse electrokardiographischer Potentiale Pflügers Arch. ges. Physiol. 255:251 1952.
18 Durrer D van der Tweel, L. H., Berreklouw S., nd van der Wey L. P Spread of activation in the left ventricular wall of the dog IV Two nd three dimensional analysis, Am. Heart J 50:860, 1955
19 Durrer D and van der Tweel, L. H. Excitation of the left ventricular wall of the dog and goat, (edited by Hecht) Ann. New York Acad. Sc. 65 779 1957
20 Durrer D., Formijne, P van Dam R. Th., Büller J., van Lier A. A. W., and Meyler F L. The electrocardiogram in normal and some bnormal conditions, Am. Heart J 61:303, 1961
21 Moore, E. N Hoffman, B. F P tterson, D F and Stuckey J H. Electrocardiographic changes due to delayed activation of the wall of the right ventricle, Am. Heart J 68:347 1964
22 Sodi-Pallares, D Brancato, R. W Pileggi, F Medrano, G. A., Bisteni, A., and Barbato, E. The ventricular activation and the vectorcardiographic curve, Am. Heart J 54:495 1957
23 Boineau, J P., Spach, M S., and Ayers, C. R. Genesis of the electrocardiogram in atrial septal defect, Am. Heart J 68:637 1964.
24 McCall, B. W Wallace A. G., and Estes, E. H Jr Characteristics of the normal vectorcardiogram recorded with the Frank lead system, Am. J Cardiol. 10:514 1962.
25 Erickson, R. V Scher A. M and Becker R A. Ventricular excitation in experimental bundle branch block, Circulation Res. 5:5 1957
26 Scher A. M Young A. C. Malmgren, A. L., and Paton, R. R. Spread of activity through the wall of the entricle, Circulation Res. 1:539 1953
27 Rodriguez, M I and Sodi-Pallares, D The mechanism of complete and incomplete bundle branch block, Am. Heart J 44 715, 1952.
28 Grant, R P Clinical electrocardiography New York, 1957 McGraw Hill Book Co Inc.
29 Medrano, G. A., Sodi-Pallares, D Marsico, F and Bisteni, A The importance of septal activation in the electrogenesis of the unipolar morphologies in bundle branch block Experimental study with total extirpation of the free ventricular wall of the blocked ventricle, Am. Heart J 57 126, 1959
30 Gould, J P Scher A. M and Hamlin, R Contribution of the right ventricular free wall to the QRS complex, Am Heart J 61:796, 1961
31 Sodi-Pallares, D Cisneros, F Medrano, G A Bisteni, A., Testelli, M R and de Micheli, A. Electrocardiographic diagnosis of myocardial infarction in the presence of bundle branch block (right and left) ventricular premature beats and Wolff Parkinson-White syndrome, Prog Cardiovas. Dis. 6 107 1963.
32 Horan, L G., Hansen, F L., and Bousquet, R M R lationship between the anatomical orientation of the interventricular septum and the manifest orientation of ventricular depolarization in dogs, Circulation Res. 10:859, 1962.

33. Hellerstein H. K., and Hamlin, R QRS component of the spatial vectorcardiogram and of the spatial magnitude and velocity electrocardiograms of the normal dog Am. J Cardiol. 6 1049 1960.
34 Burger H. C., and Vaane, J P A criterion characterizing the orientation of vectorcardiogram in space, AM HEART J 56 29 1958.
35 Schellong F Grundzuge einer klinischen Vektordiagraphie des Herzens, Berlin, 1939 Springer Verlag
36 Rijlant, R. L electrogenese global du coeur chez l'homme. Electrocardiographie vectorielle et vectorcardiographie Acta Cardiol. 13:349 1958.
37 Horan L. G Flowers, N C. and Brody D A. The limits of information in the vectorcardiogram Comparative resynthesis of body surface potentials with different lead systems, AM. HEART J 68:362, 1964
38. Horan, L. G Flowers, N C., and Brody D A. Principal factor waveforms of the thoracic QRS complex, Circulation Res. 15 131 1964

Ventricular vulnerability to paired pulse stimulation during acute coronary occlusion

Jack Han M.D Ph.D
Anna Mae Malozzi B S
*Chalmers Lyons B S***
Utica, N Y

The technique of paired pulse stimulation has been applied to decrease the effective rate and to augment the force of contraction in the ventricle.[1-3] Since the second pulse of a pair of stimuli is applied near to or in, the vulnerable period of the ventricular excitability cycle there is a risk of development of ventricular fibrillation. The risk would be even greater under certain other conditions which facilitate the induction of ventricular ectopic beats and fibrillation One obvious example is the presence of irregular perfusion of the ventricle associated with coronary heart disease.

The present experiments were performed on dog ventricles to test the effect of acute coronary occlusion on ventricular vulnerability to ectopic beats and fibrillation during paired pulse stimulation. Since the ventricular rate also influences vulnerability [4] the experiments were designed to assess the effect of acute coronary occlusion at various effective frequencies of paired-pulse stimulation

Methods

Experiments were performed on mongrel dogs ranging in weight from 10 to 20 kilograms and anesthetized by intravenous injection of sodium pentobarbital in a dose of 35 mg per kilogram Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium. The S-A node was inactivated by crushing to permit observations at slow frequencies. When a further slowing in the heart rate was necessary the right or left vagus nerve was stimulated below a crushed area. Stimuli were rectangular pulses of 2 msec duration at a frequency of 10 per second applied at a voltage sufficient to reduce the heart rate to about one cycle per second Stimuli were sometimes applied to the vagus nerve at a voltage sufficient to produce complete A V dissociation For complete occlusion of the anterior descending branch of the left coronary artery the artery was dissected free for a few millimeters near its origin to permit the application of a clamp When partial occlusion of the artery was required the artery was ligated together with a 24-gauge hypodermic needle The needle was withdrawn immediately leaving the artery constricted but not occluded

Bipolar stimulating and recording electrodes were attached to the anterior septal margin of the right ventricle on the edge of the area where ischemia extends during occlusion of the anterior descending artery Sites of stimulation and recording were

From the Masonic Medical Research Laboratory Utica, N. Y
This study was supported by [illegible] grant from the New York State Heart Assembly (Oneida County Heart Committee)
Received for publication March 16, 1964.
Address Masonic Medical Research Laboratory Utica, N. Y [illegible]
**Summer Student Fellow [illegible]

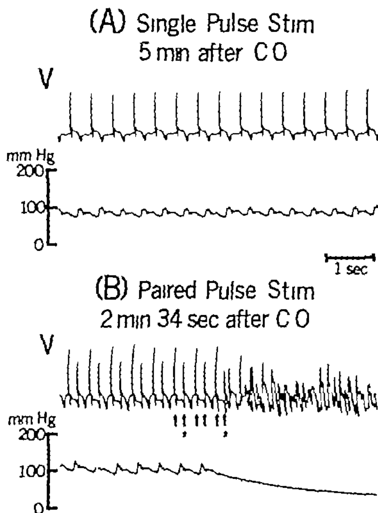


Fig. 1. Exp. 5-19-65. Fibrillation induced in the ventricle by occlusion of the anterior descending branch of the left coronary artery (C.O.) during single- and paired-pulse stimulation (A and B). The upper traces show ventricular responses, and the lower traces the aortic pressure. In the upper trace in B the time of application of the first and the second of a pair of stimuli is indicated by 1 and 2.

separated by about 6 mm. For single-pulse stimulation of the ventricle a waveform generator was used to trigger a Tektronix pulse generator which delivered square pulses of variable frequency duration and strength through an isolation transformer to the stimulating electrodes. At a chosen basic cycle length the ventricle was driven by 2 msec. pulses at two times the threshold voltage. When the ventricle was to be driven by paired pulses, the waveform generator triggered two Tektronix pulse generators which in turn, delivered paired pulses (S_1 and S_2) of 2 msec. duration to the same pair of stimulating electrodes through the same isolation transformer. At a chosen basic cycle length (S_1S_1) the interval between paired stimuli (S_1S_2) could be varied by changing the delay between the pulse generators. Electrical responses of the ventricle were recorded on a Grass polygraph at a paper speed of 25 mm. per second. The aortic pressure was also recorded on the polygraph by means of a Statham pressure transducer attached to a cannula inserted into the aortic arch.

Results

In the first group of experiments the effect of complete occlusion of the anterior descending artery on the incidence of ventricular fibrillation was assessed during single- and paired pulse stimulation. While the ventricle was driven by single or paired

electrical stimuli at a basic cycle length (S_1S_1) of 400 to 450 msec. the anterior descending artery was clamped If fibrillation occurred the clamp was removed immediately and defibrillation was accomplished by A C countershock If no fibrillation occurred the clamp was released 5 minutes after the start of occlusion. Repeat occlusion began about 20 minutes after the defibrillation or the release of the clamp on the artery The results of a representative experiment are illustrated in Fig 1 In *A* the artery was occluded while the ventricle was driven by single pulses at a basic cycle length of 430 msec. fibrillation did not develop within the 5-minute period of occlusion. In *B* the ventricle was driven by paired pulses at the same basic cycle length as that mentioned above, with an S_1S_2 interval of 185 msec. This procedure significantly increased the aortic pressure but ventricular fibrillation occurred 2 minutes and 34 seconds after the start of occlusion.

Similar results were consistently observed on repeated trials of occlusion of the anterior descending artery in 8 dogs, and the cumulative data are shown in Fig 2. Fibrillation occurred within 5 minutes after the start of occlusion in 7 of 24 trials (29 per cent) during single pulse stimulation. In these 7 trials the average time of onset was 3 minutes and 17 seconds. Fibrillation developed at an average time of 1 minute and 48 seconds after the start of occlusion in 22 of 24 trials (92 per cent) during paired-pulse stimulation. Statistical analysis indicates that the average time of onset of fibrillation is significantly different between single and paired stimulation at the level of $p < 0.01$

In the second group of experiments, the stimulus intensity of S_2 required to induce multiple responses was measured at different basic frequencies of paired-pulse stimulation before and after constriction (not occlusion) of the anterior descending artery The results of such an experiment are depicted in Fig 3 The threshold intensity of stimuli required to drive the ventricle with single pulses of 2-msec. duration was found to be 1 Ma. At each cycle length (S_1S_1) between 400 and 1,000 msec. the ventricle was first driven by single basic stimuli (S_1) of 2 Ma., and then coupled stimuli (S_2) of the same intensity were delivered to the ventricle in the refractory period of the basic responses. The S_1S_2 interval was then gradually increased until the ventricle responded to the second stimulus and further increased by increments of 5 to 10 msec. to permit observation of the incidence of multiple responses to the second stimulus. If no ectopic beats occurred the stimulus intensity was increased in increments of 1 Ma. up to 10 Ma. and a similar scan with S_2 was made at each stimulus intensity until ectopic beats developed The above-mentioned procedure was applied before and after constriction of the artery At a basic cycle length of 1 000 msec. (Fig 3,*A*) spontaneous ectopic beats developed with a stimulus intensity of 4 Ma. in the control and with 2 Ma after coronary constriction At a basic cycle length of 800 msec ectopic beats occurred with stimuli of 7 Ma. in the control and 2 Ma. after coronary constriction (Fig 3,*B*) Stimuli of 10 Ma. induced no multiple responses in the control and stimuli of 5 Ma were sufficient to induce ectopic activity during coronary constriction at the 600-msec. basic cycle length (Fig 3 *C*) Finally at 400 msec. (Fig 3,*D*) no ectopic beats developed with stimuli of 10 Ma in the control but stimuli of 8 Ma. induced

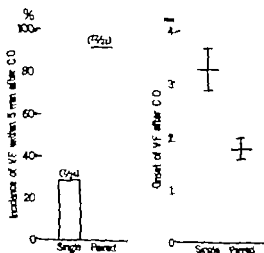


Fig 2 The cumulative data obtained from 48 trials of coronary occlusion (*C.O*) in 8 dogs. The incidence of fibrillation associated with C.O during single- and paired-pulse stimulation is shown on the left and the average time (±S.E.) of onset of fibrillation after the start of C.O is shown in the right.

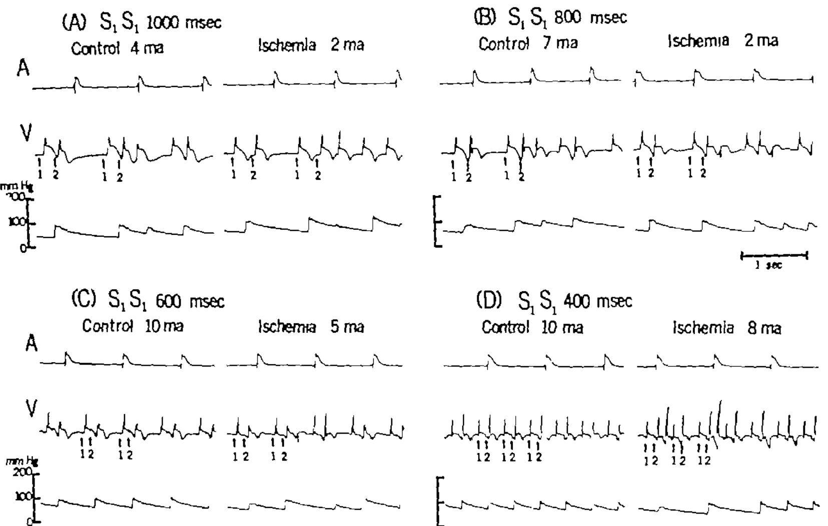


Fig. 3. Exp. 8-27-63. Spontaneous ectopic beats developed in the ventricle after paired stimuli i th control and during myocardial ischemia induced by constriction of the anterior descending artery. Basic cycle length (S_1S_1) of paired-pulse stimulation decreased from 1,000 msec. in *A* to 400 msec. in *D*. The upper traces show trial responses, the middle traces entricula responses, and the lower traces the aortic pressure. I the middle traces, th time of pplica tion of the first nd the second of pair of stimuli is indicated by *1* nd *2*.

ectopic beats after coronary constriction. In this experiment, the ectopic beats that followed the second stimulated responses could not have been propagated from supraventricular sites because the A-V conduction system was completely suppressed by intense vagal stimulation. Evidence for complete A-V block is seen in the records of atrial responses, which occurred at a regular interval independent of the irregular ventricular responses.

Fig. 4 illustrates the cumulative data of 4 experiments conducted in the same manner as that of Fig. 3. At a basic cycle length (S_1S_1) of 1,000 msec. ectopic beats occurred after S_2 stimuli of 10 Ma. or less in 3 of the 4 cases in the controls and in all 4 cases after coronary constriction. The effective stimulus intensity was less than two times the diastolic threshold value in all 4 cases after coronary constriction. At an S_1S_1 interval of 800 msec. ectopic beats developed after stimuli of 10 Ma. or less in 2 of the 4 cases in the controls and in all 4 cases after coronary constriction. The effective stimulus intensity was less than two times the diastolic threshold in 3 cases after coronary constriction. At lower S_1S_1 intervals of 600 and 400 msec., no spontaneous ectopic beats occurred in any of the controls, but ectopic responses appeared in all 4 cases after coronary constriction. In none of the cases, however, was the effective stimulus intensity less than two times the diastolic threshold.

Discussion

The results of experiments described above indicate that the risk of ventricular fibrillation is increased by paired pulse stimulation during acute coronary occlusion. The incidence of ventricular fibrilla

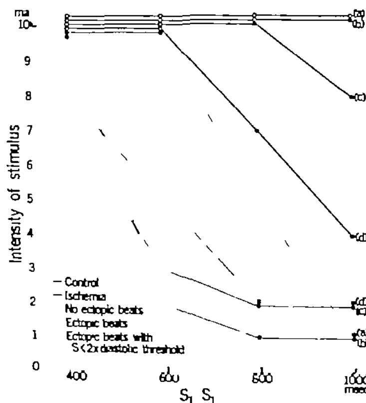


Fig. 4. Stimulus strength of paired stimuli required to induce spontaneous ectopic beats in the control and during myocardial ischemia. Data from 4 experiments. Basic cycle length (S_1S_1) is plotted on the abscissa in milliseconds and the intensity of stimuli used to test the occurrence of spontaneous ectopic beats is plotted on the ordinate in milliamperes. Each solid line connecting 4 different points indicates the control results of an individual experiment (*a*), (*b*), (*c*), or (*d*). The results obtained in each of these experiments during myocardial ischemia are shown by dotted lines.

tion was appreciably higher and the average time of onset of fibrillation after the start of coronary occlusion was significantly shorter during paired pulse stimulation than during single pulse stimulation at the same basic frequency. The present experiments also demonstrate that the hazard of inducing spontaneous ectopic beats after paired stimuli is greater at slow effective frequencies of paired pulse stimulation, as has been reported previously.[5] When a slow driving frequency was imposed during coronary ischemia, multiple responses were commonly induced at a stimulus intensity of less than twice the diastolic threshold, a strength considered to be safe for paired pulse stimulation.[6]

It has been suggested that an increased incidence of ectopic beats and fibrillation in the ventricle at slow basic frequencies is the result of an increase in the degree of asynchrony of recovery of excitability in the ventricle at slow rates. The presence of irregular perfusion of the ventricle associated with coronary occlusion is also known to contribute to increased asynchrony of recovery of excitability and to facilitate the induction of ectopic beats and fibrillation.[7] Previous studies have shown that ectopic beats were more frequently induced by coronary occlusion when the basic frequency was low.[5] This observation indicates that the selection of an optimum rate of stimulation of the ventricle at relatively higher rates is important in the presence of coronary heart disease. Since the hazard of ectopic beats and fibrillation is further enhanced by paired pulse stimulation in the presence of coronary occlusion it is particularly important to select a relatively higher frequency of paired stimuli and to limit the stimulus intensity to within the range of twice the diastolic threshold.

Summary

Vulnerability of the ventricle to fibrillation associated with acute coronary occlusion was studied during single- and paired pulse stimulation. Fibrillation was induced more frequently by acute coronary occlusion during paired pulse stimulation. The average time of onset of fibrillation after the start of coronary occlusion was significantly shorter during paired pulse stimulation. Multiple responses to the second stimulus developed more frequently at slow rates of paired pulse stimulation before and after acute coronary occlusion. The incidence of such ectopic beats was appreciably greater and the effective stimulus strength was significantly lower after coronary occlusion at all frequencies of paired pulse stimulation. The effective strength was frequently less than twice the diastolic threshold at slower frequencies after coronary occlusion. The results emphasize the importance of the selection of a relatively higher frequency and a low stimulus intensity for paired pulse stimulation of the ventricle in the presence of coronary heart disease.

We wish to thank John DeTraglia and David Millet for their technical assistance.

REFERENCES

1. Chardack, W. M., Page, A. A., and Dean, D. C.: Slowing of the heart by paired pulse pacemaking, Am. J. Cardiol. 14:374, 1964.
2. Braunwald, N. S., Gay, W. A., Morrow, A. G., and Braunwald, E.: Sustained paired electrical stimuli. Slowing of the ventricular rate and augmentation of contractile force, Am. J. Cardiol. 14:385, 1964.
3. Lopez, J. F., Edelist, A., and Katz, L. N.: Reducing heart rate of the dog by electrical stimulation, Circulation Res. 15:414, 1964.
4. Han, J., Millet, D., Chizzonitti, B., and Moe, G. K.: Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate, Am. Heart J. 71:481, 1966.
5. Han, J., DeTraglia, J., Millet, D., and Moe, G. K.: Incidence of ectopic beats as a function of basic rate in the ventricle, Am. Heart J. 72:632, 1966.
6. Cranefield, P. F.: The present status of paired stimulation and post-extrasystolic potentiation in the heart, B. II. New York Acad. Med. 41:736, 1965.
7. Han, J., and Moe, G. K.: Nonuniform recovery of excitability in ventricular muscle, Circulation Res. 14:44, 1964.

Arteriosclerosis and thrombosis in wild rhesus monkeys

K K. Chawla M.D
C D S Murthy M.D**
R. N Chakravarti M.B B S D.Phil D T M &H ***
P N Chhuttani M.D F.A.M S****
Chandigarh India

In a study of natural diseases of wild rhesus monkeys, a number of pathologic lesions of blood vessels was encountered These lesions were similar to those observed in man The presence of these lesions in the simian population in their natural habitat prompted us to study their frequency incidence morphology and relationship to sex, body weight and age blood pressure and cholesterol content of serum and aorta.

Material and methods

The study was conducted in 150 rhesus monkeys. The animals were trapped in the areas around Moradabad Saharanpur and Delhi cities in northwest India. During their brief stay in the animal house they were fed on soaked grain bananas, and bread Prior to autopsy the animals were anesthetized with an injection of sodium Pentothal and the blood pressure was recorded over the brachial pulse by auscultation. A diastolic pressure over 90 mm. Hg was considered to indicate hypertension. The approximate age of the animals was calculated from an arbitrary scale that correlated age with body weight. Their sex was noted Samples of blood were obtained from the femoral vein for estimation of total cholesterol in serum according to the technique of Zlatkis, Zak and Boyle.[1]

After the studies had been made the animals were sacrificed and a complete autopsy was performed The heart and the great vessels brain and other viscera were examined in order to detect the presence of any gross lesion. The aorta and its major branches were incised longitudinally and the internal surfaces were inspected for endothelial roughening fatty streaks, atherosclerotic plaque, and thrombus. Blocks were taken from areas of suspected lesions, as well as from normal looking segments of the aorta pulmonary subclavian carotid iliac, and basilar arteries, circle of Willis, and from the superior and inferior venae cavae. Blocks from the heart, lung kidney and brain in addition to the above-mentioned were fixed in 10 per cent neutral formaldehyde saline and paraffin and frozen sections of each tissue were prepared. The paraffin

From the Department of Experimental Medicine, Institute of Post Graduate Medical Education and Research, Chandigarh, India.
Received for publication April 8 1966.
*Registrar in Medicine.
**Former Resident in Medicine
***Assistant Professor of Experimental Medicine.
****Director-Professor of Medicine Institute of Post-Graduate Medical Education and Research, Chandigarh, India.

sections were stained with hematoxylin and eosin Mallory's PTAH for fibrin Verhoeff's iron hematoxylin with Van Gieson's counterstain for elastic and collagen fibers Alcian blue PAS for mucopolysaccharides, and Masson's trichrome for smooth muscle cells. The frozen sections were stained with oil red O for fat.

Prior to blocking a piece of thoracic aorta was stripped of its adventitial fibro-fatty tissue and weighed on a microbalance. Total cholesterol was estimated as described previously

Results

In this series there were 70 males and 80 females. Their weights varied from 1 to 10 75 kilograms, with an average of 3 56 ± 2 98 kilograms. The approximate age as calculated from body weight, ranged between 1 and 10 75 years The systolic blood pressure ranged between 60 and 160 mm Hg and the diastolic pressure, from 50 to 105 mm. Hg In a number of animals in which the systolic pressure was very low we could not record the diastolic pressure. Hypertension was detected in 5 animals. The total serum cholesterol ranged between 40 and 231 mg per 100 ml. with an average of 116 4 ± 30 7 mg The cholesterol in the aorta varied between 163 9 and 485 8 mg per 100 grams of wet tissue with an average of 248.3 ± 53 3 mg

A number of pathologic lesions were observed in different vessels. Fatty streaks most marked in the thoracic aorta were

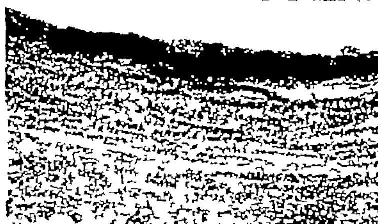


Fig 1 Frozen section of aorta showing i timal fat deposition in fatty treak. Oil red O ×150



Fig 2 Section of aorta showing an atherosclerotic plaque made up of large number of foam cells enmeshed in fibrous connective tissue. There is fraying of the nderlying elastic plates. Verhoeff iron-hematoxylin, ×150

seen in 4 animals but atherosclerotic plaques were seen in the arch of the aorta in only 1 animal (Figs. 1 and 2). Localized intimal fibrous proliferation with a variable degree of elastosis but no foam cells was seen in 18 animals (Figs. 3 and 4). As for the visceral arteries, the coronary, cerebral, and renal vessels showed this lesion in 3, 2, and 8 animals, respectively. Evidence of medial degeneration was seen in the large systemic arteries of 12 animals. There was pyknotic degeneration of the nuclei of smooth muscle cells, fragmentation of elastic lamellae, and accumulation of mucopolysaccharides. Hyaline intimal thickening involving the superficial media and forming pearly plaques was noted in the aorta and pulmonary artery in 6 animals (Fig. 5). Thrombi occluding the vessel lumen were seen in 3 animals. In one animal there was an organizing thrombus in a coronary artery. The thrombus



Fig. 3. Section of kidney showing fibrous arteriosclerosis of an interlobar artery. The internal elastic lamina is well preserved and there are newly formed elastic and collagen fibers in the plaque. Verhoeff's iron-hematoxylin, ×600.



Fig. 4. Section of the carotid artery showing fibrous arteriosclerosis. There is an increase in ground substance on account of the deposition of mucopolysaccharides. Hematoxylin and eosin, ×600.



Fig. 5 Section of the aorta showing marked intimal thickening and hyalinization of the intimal connective tissue and of the superficial media. Hematoxylin and eosin ×150.

was a fused mass of platelets, erythrocytes, and leukocytes and showed proliferating fusiform elongated cells from its base which was adherent to the vessel wall (Fig 6) A little apart from the occluded artery an area of the myocardium presented vacuolated degenerating muscle fibers, with collapse of the reticular connective tissue framework. No significant cellular reaction was noted Although it may have been an infarct due to occlusion of the coronary artery the possibility of a nonspecific focal myocarditis could not be ruled out. In a second animal the right internal carotid artery near its origin showed a marked narrowing of the lumen as a result of dense proliferation of connective tissue over the intima. The exact pathogenesis of this lesion was not clear but the possibility of its being a fully organized and recanalized thrombus in this artery was strongly considered (Fig 7) In the third animal there was a recently formed thrombus in a branch of the renal artery

Correlation of histopathologic features with other parameters

ATHEROSCLEROSIS AND FATTY STREAKS The 4 animals showing fatty streaks were between 5 and 10 years of age 3 were females and 1 was a male. Atherosclerosis was observed in a relatively young male animal The blood pressure was within normal limits in all except one which was 8½ years old and in which a pressure of 160/105 mm Hg was recorded The serum cholesterol was not elevated The level of cholesterol in the aorta was high in 2 monkeys which showed fatty streaks.

FIBROELASTIC ARTERIOSCLEROSIS. Of the 18 animals affected 10 were 1 year old and the remainder were between 7 and 10 years old Females accounted for 11 cases, and males for 7 The blood pressure remained within the normal range in all except 2 animals which had hypertension. The serum cholesterol values were usually not elevated but in 1 animal the value was 184 mg per 100 ml The cholesterol content of the aorta was high in only 1 monkey which had fibrous intimal thickening of the coronary arteries

MEDIAL DEGENERATION AND HYALINE INTIMAL THICKENING In this series 8 of 12 animals having medial degeneration were young 5 were males and 7 were females. The blood pressure was high in only 2 animals. Although the level of cholesterol in the serum was high in 1 of these 2 animals, that in the aorta was normal in all Hyaline intimal thickening was detected in 6 animals 5 of which were females and all belonged to the higher age group The sixth animal was a male and had hypertension The levels of cholesterol in the serum and in the aorta were high in 2 monkeys, both females

THROMBOSIS Two of the 3 animals inflicted with thrombosis were young and the third one was fairly old. There were



Fig. 6 Section of heart showing an occluding thrombus in an intramural branch of the coronary artery. The thrombus is adherent to the artery wall and is organizing. Hematoxylin and eosin ×600.

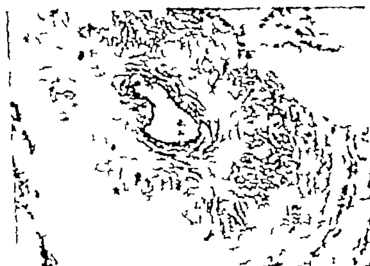


Fig. 7 Section of extracranial portion of an internal carotid artery showing extreme narrowing of lumen as result of massive formation of dense connective tissue over the intima. The internal elastic lamina is seen deeply embedded in the artery wall. The fibrous thickening of intima may be the end result of an organized and re-canalized thrombus. Hematoxylin and eosin, ×150.

2 females and 1 male. The blood pressure was normal and cholesterol values in the serum and aorta were not elevated.

Discussion

The present study has shown that rhesus monkeys in their natural habitat also suffer from several arterial diseases, the frequent conditions being fibrous arteriosclerosis and medial degeneration. Other less frequent conditions are fatty streaks and atheroscleroma of the aorta and thrombotic occlusion of the internal carotid, coronary, and renal arteries. In a previous communication Chakravarti and Chawla reported that wild rhesus monkeys develop mural thrombosis also.

In an attempt to explore the possible mechanisms responsible for these lesions a number of parameters, such as age and body weight, sex, blood pressure, level of cholesterol in the serum and aorta, were

studied It appeared that the spontaneous lesions of fatty streaks and atherosclerosis in monkeys were not directly influenced by sex blood pressure, and serum cholesterol but age (body weight) and amount of cholesterol in the aorta may play some role. This can be suggested because 3 of 5 animals were old and 2 had a high level of cholesterol in the aorta. It may be possible that tissue senility influences atherogenesis by altering the biosynthesis of lipids in the arterial wall and by depressing various enzymatic reactions.[4]

In the production of fibrous arteriosclerosis it was observed that young as well as old animals were affected and that there was no particular sex predilection. The blood pressure was high in only 2 of 18 animals The levels of cholesterol in the serum and in the aorta were also within normal limits in almost all cases. Therefore, it seems to be reasonable to conclude that this type of lesion is mostly independent of the factors enumerated The other important possibility is that this lesion originated through organization of mural thrombi The previous study of Chakravarti and Chawla on monkeys showed that mural thrombi were incorporated into the intima of arteries and produced intimal thickening by fibrous organization. Also in other experimental studies in rabbits and dogs it was observed that organization of vascular thrombi caused arteriosclerotic lesions.[5,6] These evidences may be taken to suggest that a major fraction of these lesions could be the end result of organized mural thrombi in arteries.

In the causation of hyaline intimal thickening and medial degeneration, multiple factors appeared to play their parts. In the former group 5 of 6 were old female monkeys, 1 of which had hypertension. Similarly of those showing medial degeneration without pearly plaque formation 3 animals were old females and had hypertension. It appears, therefore, that senile change in the arteries coupled with hypertension are factors in the pathogenesis of this type of vascular lesion. The significance of these lesions in female monkeys is not clear however A number of young animals with normal blood pressure also had degenerative medial lesions, one of the more plausible causes for which could be malnutrition particularly a deficiency of ascorbic acid and pyridoxine. These deficiencies are known to affect the ground substance and the fibrillar structures of the vessel wall causing hyaline intimal thickening and degeneration of smooth muscle and elastic plates in the media.[7,8]

The animal showing coronary thrombosis was an old female with hypertension. She had normal levels of cholesterol in the serum and aorta. Although the exact mechanism of thrombosis is not clear the possibility is that old age and hypertension acted as predisposing factors. The other 2 animals showing carotid and renal artery thrombosis were young and had normal blood pressures. They too did not have an elevated level of cholesterol in the serum and aorta. In the absence of any visible pathologic lesion in the vessel wall in these animals, one could postulate some intrinsic disturbance of the thromboplastin-antithromboplastin mechanism or fibrinolysin antifibrinolysin equilibrium responsible for this condition.

Summary

In a survey of spontaneously occurring vascular diseases of wild rhesus monkeys it was observed that, of 150 animals, 4 showed fatty streaks and 1 showed atherosclerosis of the aorta. Fibrous arteriosclerosis was detected in 18 animals. Medial degeneration and hyaline intimal thickening was seen in 18 animals, and occluding arterial thrombi in 3 animals. Hypertension was observed in 5 animals. An attempt was made to correlate the pathologic findings in these animals with age and body weight, sex blood pressure and the level of cholesterol in the serum and the aorta.

We wish to thank M Ram Swaroop and M Mohan Singh for technical assistance, and M G. S. Sekhon for preparing the photomicrographs.

REFERENCES

1 Zlatkis, A., Zak, B., and Boyle, G. J : A new method for the direct determination of serum cholesterol, J Lab. & Clin. Med. 41:486 1953
2. Sarkar A. K., and Chakravarti, R. N : Blood and tissue lipids in rabbits subjected to intermittent starvation and f t feeding, Indian J Exper Biol. 3:265 1965.
3. Chakravarti, R. N and Chawla, K. K :

Spontaneously occurring mural thrombi in arteries of Macaca mulatta, J Atheroscler Res. 6:455 1966.

4. Adams, C. W. M. Arteriosclerosis in man, other mammals and birds, Biol. Rev 39:372, 1964.

5. Chakravarti, R. N. and Srivastava, G. N. Fate of organized experimental arterial thrombi in normal and atherosclerotic vessels of the rabbit kidney Indian J Med. Res. 52:258, 1964.

6. Sahni, V. K., Chopra, R. K., Chitambar A. S and Chakravarti, R. N An experimental study of vascular repair using autogenous and synthetic vessel graft, Proceedings, International Congress of Diseases of the Chest, Copenhagen, 1966.

7. Willis, G. C. Ascorbic acid deficiency and atherosclerosis, Canad. M A. J 77 106, 1957

8. Rinehart, J F and Greenberg L. D Arteriosclerotic lesions in pyridoxine-deficient monkeys, Am. J Path. 25:481 1949

The mechanical nature of the heart as a pump

*Robert M Anderson M.D.**
James M Fritz M.D.
James E. O'Hare M.D.
Tucson Ariz.

An extracorporeal heart replacement pump has been developed which mimics cardiac function without any adjustments or controls. A comparison of the function of this pump with that of the heart indicates that its mechanical characteristics are the same as those of the heart. The inadequacy of conventional basic hemodynamic principles to explain the findings shakes the very foundation of cardiovascular physiology. A new more realistic concept of basic hemodynamics is presented.

The mechanical pump (Fig 1) has three basic hydraulic characteristics. It will be shown that the heart in all of its complexity also has only these three essential basic pump characteristics (1) It fills passively (it does not suck at its inlet) (2) Its atria allow continuous uninterrupted venous inflow (3) It has an intermittent or pulsatile outflow. Incomplete understanding of these three characteristics of the heart is evident in past medical writings.

Pulsatile blood flow was known to be of benefit in 1937 when Swindle[1] showed that it prevented intravascular agglutination and allowed diffuse generalized perfusion of tissue. He indicated that the transfer of materials between the extravascular space and the capillary bed is facilitated by pulsatile blood flow. Wilkens, Regelson and Hoffmeister[ ] have reviewed the evidence of the importance of pulsatile blood flow. Lillehei[ ] showed by motion pictures that there was a decrease in the number of vessels with flow in them as the time increased using conventional nonpulsatile cardiopulmonary bypass. The other two characteristics of the heart have received less consideration. Norton,[4] Liotta,[ ] [7] and Seidel[8] and their associates in recent attempts at cardiac replacement, have used nonsucking pumps. They use them to prevent undue negative pressure in the vena cava and allow the heart replacement filling rate to be determined by the venous pressure. Wiggers and Katz[9] give evidence that the atria have a significant effect in normal physiology. Liotta,[6] Akutsu[1] and Atsumi[11] and their colleagues reported the incorporation of atria in cardiac replacement pumps but do not indicate whether these atria allow uninterrupted venous inflow. Most investigators in the field of mechanical heart replacement use pumps which are deficient in one or more of these three characteristics.[12,13] The importance of the understanding of these three basic mechanical characteristics to clinical cardiology, cardiac surgery, and the develop-

From the Department of Zoology, University of Arizona, and the Department of Surgery, Tucson Medical Center, Tucson, Ariz.
Research supported by the American Heart Association branches of Santa Barbara County, California, Orange County, California, and Arizona.
Pump constructed by grant from The Heller Foundation of Tucson, Ariz.
Received for publication April [illegible]
*Address: [illegible] East San Carlos Place, Tucson, Ariz. [illegible]

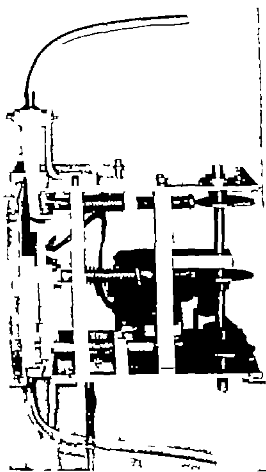


Fig 1A A pulsatile nonsucking pump.

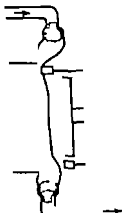


Fig 1B Diagram of the pulsatile nonsucking pump.

ment of a mechanical heart replacement makes this report timely

Description of pump

The cardiac replacement pump (Fig 1) consists of a ventricle which passes through three synchronized cam-driven plungers. The outside plungers are ½ inch wide and act as inlet and outlet valves. The 8-inch wide center plunger acts as an impeller The proximal 4 inches of the ventricle above the inlet valve acts as an atrium The pump has three mechanical characteristics

1 Passive filling The nonsucking nature of the pump is due to the characteristics of the ventricle. A cutaway diagram in Fig 2 shows the thin rubber ventricle with a flat cross section. This flat configuration prevents any sucking by rebound to a

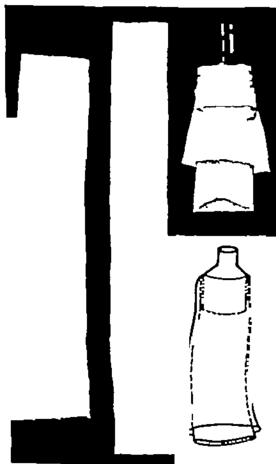


Fig 2. Construction of nonsucking pump ventricle *Inset* Cutaway diagram of pump ventricle.

round cross section after the ventricle has been compressed. A cloth covering is added for strength Fig 3*A* shows the lack of diastolic sucking of such a ventricle in comparison to the sucking of the resilient tubing used in conventional roller and finger pumps when their inlets are occluded The output range at 80 compressions per minute with up to 12 cm of venous filling pressure from tubing of ½-inch I D is from 0 to 4,200 c c per minute Non sucking pumps, in contrast to ones that suck at their inlets, do not produce a given flow rate but merely pump out any fluid that comes in within their operating range (Fig 3*B*) If 50 c.c. per minute runs into the pump 50 c.c. per minute is pumped out. If 4,200 c.c. per minute runs in 4 200 c.c. per minute is the output. On the other hand the output of sucking pumps is dependent upon the speed or rate of the pump Changes in the rate of the pump

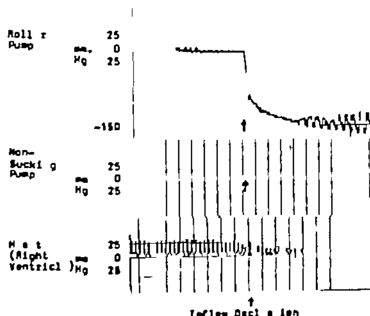


Fig 3A Absence or presence of negative pressure generated by pumps after inflow occlusion.

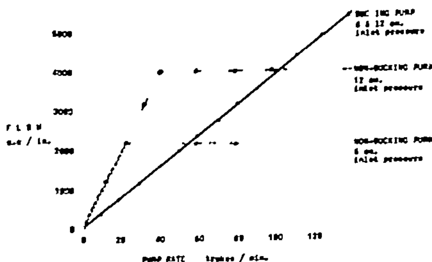


Fig 3B Pump output with sucking nd nonsucking pumps with variation in pump rate and inflow pressure

with nonsucking pumps merely change the stroke volume not the minute output. Non-sucking pumps are passive to their output. The flow rate is completely dependent upon outside factors which determine the flow rate to the pump Fig 3*B* shows findings obtained by changing the pump rates and inflow pressures of these two types of pumps. This illustrates the difference in their output regulation

II Atrial effect The hydraulic effect of the atrium is that it allows uninterrupted inflow of fluid from the veins to the pump A procedure which demonstrates the mechanism of this feature is shown by Figs. 4 and 5

In Fig 4,*A* a tube ½ inch in diameter is placed into a reservoir of water with the tubing outlet 12 cm below the level of the fluid The fluid in the bottle at the

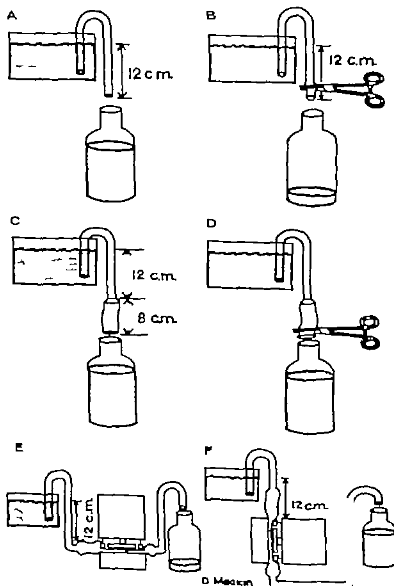


Fig. 4 *A* Flow of fluid through ½-inch tubing at 12 cm. of pressure for 1 minute. *B* Interrupted flow with tubing unclamped for a total of 45 seconds. *C*, Continuous flow with atrium *D* Interrupted flow with atrium. *E*, Nonsucking pump flow rate with 12-cm. inlet pressure with no atrial effect. *F* Nonsucking flow rate with 12-cm. inlet pressure using an atrium.

tubing outlet represents the 4 200 c c per minute that will flow in such a system If the flow is now periodically interrupted by clamping the tubing 80 times a minute for occlusion periods totaling only a fourth of the time the flow is reduced to 800 c.c per minute (*Fig 4,B*) This decrease in flow is more than that caused by the absence of flow during the periods of interruption since each period of interruption is followed by a period of decreased flow while the fluid is accelerating to its original rate (Fig 5) If the frequency of the interruption is very great *there is almost no* flow even though the tubing is open most of the time. The area beneath the flow velocity lines of Fig 5 indicates the relative flow rates in continuous and interrupted flows at the same pressure.

The two systems represented by *A* and *B* of Fig 4 are now modified to include a 4-inch segment of thin distensible rubber tubing at the tube outlets (Fig 4 *C* and *D*) If fluid is allowed to flow in an uninterrupted manner the flow rate, as before will be 4 200 c.c. per minute (Fig 4 *C*) It is shown however in Fig 4,*D* that interruption of outflow in such a system does not reduce the minute flow rate as it did in Fig 4,*B* It remains 4,200 c.c per minute This is because dilation of the distensible segment allows the flow in the half inch tubing to continue during periods of clamping The flaccid tubing acts as an atrium which distends when its outlet is occluded and is emptied by gravity drainage and by fluid flowing through it when the clamp is removed *E* and *F* of Fig 4 show the effect of flow rates with a nonsucking pump with and without this atrial effect. In Fig 4 *F* the 4-inch segment of flaccid distensible tubing is above the pump inlet, so that it distends when the inlet valve is closed and empties when it opens. This allows the pump to put out 4 200 c.c. instead of the 800 c.c. per minute seen in Fig 4,*E*, wherein the pump systole interrupts the flow of fluid in the tubing In Fig 4,*E*, the position of the atrium eliminates the gravity emptying when the valve is open by eliminating the atrial effect and results in a decreased (800 c.c. per minute) flow rate. To duplicate the 4 200 c.c. flow rate with the interruption of flow without such an atrium required the elevation of the inlet pressure to 48 mm. Hg Thus if there are *no atria it is necessary to have four times* the normal venous pressure to get the same output, from a nonsucking pump as when atria are present.

III Pulsatile outflow A pulsatile outflow at a fixed rate of 80 per minute is provided by intermittent compression of the ventricle by the cam-operated press Ventricular systole occupies a fourth of the cycle

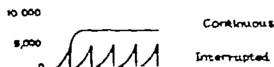


Fig 5 Comparison of continuous and interrupted flow rates and volumes. Shaded area represent volume.

Procedures

Twenty seven mongrel dogs were used In 15 dogs both the left and right sides of the heart were bypassed with nonsucking ventricles placed in the pulsatile pump The dog's own lungs were thus used for oxygenation The heart was exposed through a median sternotomy Tubing with a ¾-inch I D drained blood from each atria to its respective pump Infusion from the two pumps was through pulmonary artery and aorta cannulae having an I D of ¼ inch The pump inlets were placed at the level of the inferior aspect of the atria in order to have the prosthesis in the same hydrostatic position as the dog's own heart. Bypass was established by turning on the pump unclamping the venous drainage tubes, and then fibrillating the heart. Termination of bypass was by defibrillating the heart, clamping the atrial cannulae, and then turning off the pumps. Bypass periods up to 14 hours were maintained No adjustment or regulation of the pump rate was made at any time.

Eleven other dogs were put on cardiopulmonary bypass using gravity drainage

*One of the 15 experiments was done as demonstration for surgical staff meeting at the Tacoma Medical Center Hospital.

to a bubble oxygenator and a pump with a single ventricle. The inlet of the ventricle was placed at the desired level of blood in the oxygenator. Bypass was utilized for periods up to ? hours. No pump adjustments or regulations were made.

One attempt was made to perform a right heart bypass alone using a single ventricle and pumping from the right atrium to the pulmonary artery. This bypass left the lungs and left ventricle functioning.

To correlate findings from these procedures with normal physiology, mean vascular pressure experiments are included later under the heading *Cardiac Output*.

Findings

Fifteen dogs placed on cardiac bypass with two pulsatile nonsucking pumps with atria were observed to maintain normal mean arterial blood pressure and to react in a normal way to stimuli which normally cause alterations in blood pressure and circulatory rate. They also maintained normal blood volume balance between the systemic and pulmonary circuits. *This duplication of cardiac action occurred without any pump adjustments being made.*

Figs. 6, 7, and 8 from Dog No. 14 are typical of tracings obtained from all of the animals on two-pump bypass. Fig. 6 shows the arterial blood pressure after the onset of bypass, with the same mean pressure being maintained as before bypass. The systolic pressure on bypass is higher and the diastolic pressure is lower because the pump rate is slower than the heart rate had been before bypass. The pump being slower has a greater stroke output at the same flow rate. Fig. 7 shows the decrease in arterial blood pressure while on bypass, after 400-c.c. hemorrhage followed by the increase in blood pressure after administration of epinephrine. The epinephrine effect wore off in approximately 5 minutes. The resulting hypotension was then gradually corrected by giving back the 400 c.c. of blood. Fig. 8 shows the effect of Arfonad on the blood pressure in the same animal while on bypass. Six minutes after hypotension from Arfonad, epinephrine again increased the blood pressure. These changes in arterial blood pressure parallel in each instance the changes in the rate of blood flow as observed by the amount of diastolic distention of the pump ventricles. All of the changes demonstrated here were independent of the pump since it was not adjusted but was passive and pumped out whatever came to it.

Blood volume balance between the pulmonary and systemic circuits was maintained at all times in every case without any need for adjustment of the pump. This was evident since no pulmonary edema or hypoxia developed such as that which occurs so easily with sucking pump systems. To demonstrate the effectiveness of this nonsucking pumping system in preventing pulmonary edema from imbalance of the two pumps, the following experiment was performed during two of the procedures. Blood was removed from the aorta and injected into the pulmonary artery in increments of 25 c.c. until an amount equal to more than the entire volume of blood had been exchanged over a 10-minute period. This caused no change in compliance and no pulmonary edema or evidence of any imbalance in the volumes between the two systems. The distensibility and resistance of the two systems determined the blood volume balance between them. For example, if the pulmonary and systemic circuits are in equilibrium, there is essentially equal right and left output. If for any reason there is a shift of blood from the systemic circuit to the pulmonary compartment, the mean systemic pressure will fall and the mean pulmonary pressure will rise. This causes a slowing down of blood returning to the right heart, and a speeding up of blood coming to the left heart. Since both pumps put out whatever comes to them, the left ventricular output then exceeds the right until the old equilibrium is again established. This is simply hydraulic cause and effect and is not dependent on any reflex or adjustment when nonsucking pumps are used. This explains why in intact circulatory systems there can be loss of fluid by loss of water in exhaled air, gain of fluid from the gastrointestinal tract, addition of blood by transfusion to the systemic circuit, and large left-to-right or right-to-left shunts with no imbalancing of the volume equilibrium between the two circuits. By contrast, pumps which suck at their inlets have their output determined by their rate, so that

some types of hypertension and congestive failure were defined in terms of mean vascular pressure

STUDY OF EFFECT OF MEAN VASCULAR PRESSURE ON CARDIAC OUTPUT In anesthetized dogs in various physiologic states, circulation was stopped by inducing ventricular fibrillation by a relatively long low voltage shock. As cardiac output stopped the arterial pressure fell and the venous pressure rose so that they approached the same pressure as the fluid became stationary The resulting mean vascular pressure in the vascular system was recorded The circulation was then restarted by defibrillating the heart. After fibrillation 10 to 15 seconds was all that was necessary for the pressure to equilibrate except for a very small gradient. Fig 9 shows a normal mean vascular pressure of 16 mm Hg in a dog with normal arterial blood pressure The dog was then resuscitated and repetition of fibrillation after recovery periods consistently gave a pressure of 16 mm Hg This has been shown in our laboratory to be the normal mean vascular pressure in dogs. Fig 10 shows the blood pressure response after intravenous injection of 1 c c. of 1 10 000 epinephrine After a maximal response of elevated blood pressure had been obtained the heart was fibrillated and the mean vascular pressure was recorded at 32 mm Hg or twice normal Fig 11 shows low mean vascular pressure after loss of blood The same mean vascular pressure and blood pressure responses were obtained in animals with hearts replaced by nonsucking pumps. In these cases the flow rates as seen by increases and decreases in diastolic pump filling correlated with elevations and decreases in arterial blood pressure. This shows that the increased circulatory rate (increased cardiac output) after the use of epinephrine is due to a rise in mean vascular pressure from increased tone of the vascular system The cardiac effect of epinephrine in increasing the heart rate and the strength of contraction prevents the heart from failing in this situation. However the heart remains passive in so far as determining the circulatory rate.

2 Peripheral resistance The circulatory rate is inversely proportional to changes in peripheral resistance The previous data (Figs. 6-11) support the concept that blood pressure elevation from vasopressors is due to increased mean vascular pressure and not to an increase in resistance. The blood pressure elevation is concurrent with increased circulatory flow rate instead of a decreased rate that would accompany a blood pressure elevation from increased arteriolar resistance. The mechanical effect

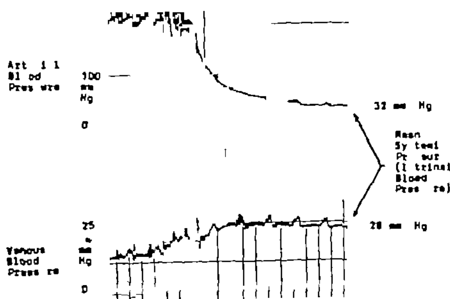


Fig 10 Dog arterial nd venous blood pressure on fibrillation An elev ted mea vascular pressure ft administration of adrenaline

of exercise increases cardiac output by decreasing peripheral resistance. This occurs when the contracting muscles around veins containing valves pump blood through channels the resistance of which would otherwise slow the flow.

The cardiac effect of drugs, changes in heart rate, and Starling's law in new perspective

Increased cardiac contraction in response to drugs, increased strength of myocardial contraction to increased diastolic filling (Starling's law), and increased heart rate are all observed in situations of increased cardiac output. They have been misunderstood to be the cause of increased cardiac output because they occurred concomitantly with it. With the previous findings it is seen that with a pump which has a fixed rate and one that cannot react to drugs, etc., circulatory responses are kept intact. They occur without any of the above-mentioned responses. These three are simultaneous responses to situations with increased circulatory rate and do have a physiologic benefit in the conservation of energy expended by the heart. If the heart contracted with maximum strength all of the time, the circulation rate would vary in a normal fashion to all situations, but this would be a great waste of energy most of the time. If, however, the heart contracted at minimal strength all of the time, it would be in failure in high-output situations. The responses which increase the strength of myocardial contraction insure adequate strength to prevent failure during rapid circulation and the conservation of energy by the heart during periods of slow circulation.

Augmentation of this experimental evidence is found in the following clinical examples of the independence of the output and heart rate. Distance runners may have slow heart rates in the presence of high output. Variation in cardiac output occurs with fixed heart rates from cardiac pacemakers. Tachycardia may occur in hypovolemia with low output. High-output hypertension may occur with a slow heart rate.

It is seen, therefore, that the rate of circulation (cardiac output) is regulated by the extracardiac factors, mean vascular pressure and vascular resistance. Changes in heart rate and strength of contraction insure absence of failure at high outputs. The stroke volume of the nonfailing heart is inversely proportional to heart rate for any given circulatory rate. Stroke volume is determined by these two factors rather than being a determinant of them.

The nonfailing heart, in all of its com

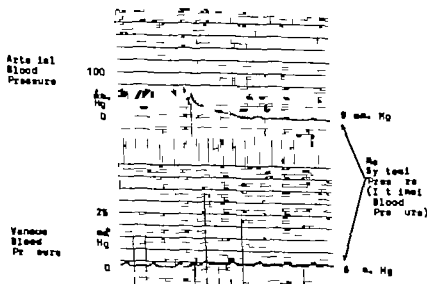


Fig. 11. Dog arterial and venous blood pressure equilibration to low mean vascular pressure after loss of 400 c.c. of blood.

plexity is a passive pump pumping out what comes to it without any regulation over the rate of circulation

Conclusions

1. A cardiac replacement pump which duplicates cardiac function in all physiologic states with no controls or adjustments has been used in dogs.

2. The essential characteristics of the heart and also of this replacement pump have been demonstrated: (1) They are nonsucking pumps, (2) they have a pulsatile outflow, and (3) there is uninterrupted venous flow into them.

3. A new concept of basic hemodynamics is presented which gives better insight into the passive nature of the heart in the regulation of cardiac output and of blood volume between the lungs and systemic circuits.

4. The atria are found to have their physiologic benefit in allowing continuous venous flow to the heart in the presence of an intermittent pumping system.

5. Cardiac output (in the presence of a nonfailing heart) is shown to be determined completely by extracardiac factors.

REFERENCES

1. Swindle, P. F.: Occlusion of blood vessels by agglutination of red cells, mainly as seen in tadpoles and very young kangaroos, Am. J. Physiol. 120:59, 1937.
2. Wilkens, H., Regelson, W., and Hoffmeister, F. S.: The physiologic importance of pulsatile blood flow, New England J. Med. 26:443, 1962.
3. Lillehei, C. W.: Motion picture shown at Los Angeles Heart Association meeting in 1961.
4. Norton, S. H., Akutsu, T., and Kolff, W. J.: Artificial heart with anti-vacuum bellows, T. Am. Soc. Artif. Intern. Organs 8:131, 1962.
5. Liotta, D., Tallani, T., Giffoniello, A., Dehlma, F., Liotta, S., Lizarraga, R., Tolocka, L., Panano, J., and Biancotti, E.: Artificial heart in the chest: Preliminary report, T. Am. Soc. Artif. Intern. Organs 7:318, 1961.
6. Seidel, W., Akutsu, T., Mirkovitch, V., Brown, F., and Kolff, W. J.: Air-driven artificial hearts inside the chest, Tr. Am. Soc. Artif. Intern. Organs 7:378, 1961.
7. Liotta, D., Hall, C. W., Cooley, D. A., and DeBakey, M. E.: Prolonged ventricular bypass with intrathoracic pumps, Tr. Am. Soc. Artif. Intern. Organs 10:154, 1964.
8. Wiggers, C. J., and Katz, L. N.: The contour of the ventricular volume curves under different conditions, Am. J. Physiol. 58:439, 1922.
9. Liotta, D., Crawford, E. S., Cooley, D. A., DeBakey, M. E., Urquia, M., and Feldman, L.: Prolonged partial left ventricular bypass by means of an intrathoracic pump implanted in the left chest, Tr. Am. Soc. Artif. Intern. Organs 8:90, 1962.
10. Akutsu, T., Mirkovitch, V., Topaz, S. R., and Kolff, W. J.: Silastic sac type of artificial heart and its use in calves, T. Am. Soc. Artif. Intern. Organs 9:281, 1963.
11. Atsumi, L., Hori, M., Ikeda, S., Sakurai, Y., Fujimori, Y., and Kimoto, S.: Artificial heart incorporated in the chest, T. Am. Soc. Artif. Intern. Organs 9:292, 1963.
12. Barila, T. G., Nunn, D. B., and Woodward, K. E.: A blood pump powered and controlled by a fluid amplification system, Tr. Am. Soc. Artif. Intern. Organs 8:30, 1962.
13. Burney, R. G., Pierce, W. S., Williams, K. R., Boyer, H. H., and Kirby, C. K.: Studies on an artificial heart controlled by venous pressure servomechanism, T. Am. Soc. Artif. Intern. Organs 9:299, 1963.
14. Hastings, F. W., Potter, W. H., and Holter, J. W.: Artificial intracorporeal heart, T. Am. Soc. Artif. Intern. Organs 7:323, 1961.
15. Hastings, F. W., Holter, J. W., and Potter, W. H.: A progress report on the development of a synthetic intracorporeal blood pump, T. Am. Soc. Artif. Intern. Organs 8:116, 1962.
16. Hiller, K. W., Seidel, W., and Kolff, W. J.: A servomechanism to drive an artificial heart inside the chest, Tr. Am. Soc. Artif. Intern. Organs 8:125, 1962.
17. Kimoto, S., Atsumi, K., Sakurai, Y., Yamazaki, Z., Imayama, T., Fujimori, Y., and Uchida, R.: Studies on the artificial heart driven with controlled gas pressure device on the pressure generator for universal use, Tr. Am. Soc. Artif. Intern. Organs 10:66, 1964.
18. Kusserow, B. K.: The use of a magnetic field to remotely power an implantable blood pump: Preliminary report, Tr. Am. Soc. Artif. Intern. Organs 6:292, 1960.
19. Pierce, W. S., Burney, R. G., Boyer, M. H., Driscoll, R. W., and Kirby, C. K.: Problems encountered in experiments during the development of our artificial intrathoracic heart, T. Am. Soc. Artif. Intern. Organs 8:118, 1962.
20. Bloom, W. L.: Diastolic filling of beating excised heart, Am. J. Physiol. 187:143, 1956.
21. Henderson, Y.: The volume curve of the ventricles of the mammalian heart and the significance of this curve in respect to the mechanism of the heart beat and the filling of the ventricle, Am. J. Physiol. 16:325, 1906.
22. Mitchell, J. H., Gilmore, J. P., and Sarnoff, S. J.: The transport function of the atrium. Factors influencing the relation between mean left atrial pressure and left ventricular end-diastolic pressure, Am. J. Cardiol. 9:237, 1962.
23. Mitchell, J. H., Gupta, D. N., and Payne, R. M.: Influence of atrial systole on effective ventricular stroke volume, Circulation Res. 17:11, 1965.
24. Starling, E. H.: Some points in the pathology of heart disease, Arris and Gale Lectures, Lancet 1:652, 1897.

25. Starr I and Rawson, A. J Role of static blood pressure in abnormal increments of venous pressure, especially in heart failure Theoretical studies on improved circulation schema whose pumps obey Starling law of the heart, Am. J M Sc. 199:27 1940.

26. Guyton, A. C., Polizo, D nd Armstrong G. G.: Mean circulatory filling pressure measured immediatel after cessation of heart pumping Am. J Physiol. 179:261, 1954.

27 Anderson R. M I trinsic blood pressure, Circulation 13:641 1956.

Case reports

Hypertrophic subaortic stenosis in the aged

Donald L. Warkentin, M.D.
Michael E. Korns, M.D.
Iowa City, Iowa

The recognition of idiopathic hypertrophic subaortic stenosis (IHSS) as a distinct clinical and pathologic cause of obstruction of the left ventricular outflow tract is relatively recent. Although it was first described in 1907, 50 years elapsed before physicians became aware of its importance. Perhaps its very nature as a dynamic lesion makes it more difficult to recognize than the more common acquired and congenital causes of obstruction of the left ventricular outflow tract. Within the past several years there have been many attempts to elucidate the pathogenesis of this disease, but still there is scant knowledge in regard to its cause and natural history. Presumably, IHSS may be either congenital or acquired, since it has occurred among the stillborn, among members of the same family, and among adults who previously had been well. This report adds to the information about the natural history of IHSS and records, to our knowledge, the case of the oldest person in which a premortem diagnosis has been well substantiated by both cardiac catheterization and angiocardiographic studies.

Case history

A 67-year-old retired farmer had had exertional dyspnea for 6 years. This gradually became worse and was accompanied by intermittent attacks of severe breathlessness which were initiated by stooping over at the waist, by squatting, or by kneeling. In 1962, he consulted his physician and was told that he had a heart murmur. Until this time several physical examinations had failed to reveal a murmur. From 1963 until he died, he had short attacks of syncope which lasted 2 or 3 minutes, and which were associated with severe shortness of breath. During the last year he had increasingly severe dizziness on exertion and noticed that large meals sometimes brought on his symptoms. A roentgenogram of the chest showed cardiac enlargement, and he was hospitalized.

His history showed that he had had two laminectomies in 1945 because of numbness in his right leg. In 1961 he had a transurethral resection of the prostate gland for hyperplasia. For many years he had had throbbing headaches which were accompanied by nausea and vomiting and which were relieved by one of the ergot drugs. The family history was not remarkable.

At physical examination the blood pressure was 130/68 mm. Hg and the pulse rate was 74 per minute. There were a few ectopic ventricular contractions. There was a minimal degree of sclerosis of the retinal arterioles and minimal loss of hearing bilaterally. The left border of cardiac dullness was percussed 1 cm. outside the mid-clavicular line in the fifth intercostal space. Palpation of the chest revealed a double apical impulse, a definite left ventricular thrust, and a systolic thrill in a local area between the apex and the third intercostal space at the left sternal border. The first heart sound was faint and was followed immediately by a Grade 4/6 medium-pitched, blowing holosystolic murmur which was best heard at the apex, but which also radiated toward the axilla and the left sternal border. A third heart sound was present. The second heart sound in the pulmonic area was slightly increased in intensity. The edge of the liver could barely be palpated, but was not tender. The peripheral arterial pulses were of normal volume and con-

From the Departments of Internal Medicine and Pathology, University of Iowa College of Medicine, Iowa City, Iowa.
Received for publication Feb. 14, 1966.
*Assistant Professor of Internal Medicine.
**Instructor in Pathology.
Requests for reprints should be addressed to Donald L. Warkentin, M.D., Department of Internal Medicine, University Hospitals, Iowa City, Iowa, 52240.

tour. Although there was a brisk rise in the anacrotic limb of the radial pulse w...

Laboratory examination was normal, except for a roentgenogram of the chest which showed equivocal cardiac enlargement, and an electrocardiogram which showed left ventricular hypertrophy.

A tentative diagnosis of rheumatic heart disease with mild congestive heart failure was made and digitalization was begun on Sept. 11, 1965. On September 13 he became comatose and went into shock. An electrocardiogram made shortly thereafter showed atrial fibrillation with a ventricular rate of approximately 95 per minute. After vasopressors were administered, his blood pressure could be measured but he was semicomatose for approximately 30 minutes. The atrial fibrillation reverted spontaneously to sinus rhythm. Serial enzyme determinations and electrocardiograms did not indicate any acute cardiac damage. Several days later he had a similar attack; he was dizzy and had blurred vision, but did not lose consciousness. Because of this, he was transferred to University Hospitals, where cardiac catheterization was performed on September 24.

Cardiac catheterization (Table I) and left ventricular angiograms indicated the presence of hypertrophic subaortic stenosis and mitral regurgitation. The left ventricular pressure tracing showed the characteristic subvalvular chamber with a peak systolic pressure gradient of 80 mm. Hg (Fig. 1). Biplane angiocardiograms confirmed the presence of a subvalvular chamber, hypertrophy of the left ventricular wall, and a severe degree of mitral regurgitation (Fig. 2). No premature ventricular contractions which might have caused transient mitral regurgitation were observed during the injection of dye.

On September 27 the patient again went into shock, lost consciousness, and began to develop severe left ventricular failure with pulmonary edema. Despite vigorous treatment with intermittent positive pressure breathing, vasopressors, and beta adrenergic receptor blockade, he died.

Necropsy. The heart weighed 530 grams. That the left ventricle was the seat of a severe degree of concentric hypertrophy was apparent even before the heart was opened. Both atria and the right ventricle were dilated, and the right ventricle was hypertrophied. The cavity of the right ventricle appeared to be diminished by diffuse encroachment by the hypertrophied left ventricle (Fig. 3). Except for dilatation of their rings, the tricuspid and pulmonic valves were normal.

There was no endocardial thickening in the left atrium and, as viewed from above, the mitral valve appeared to be normal. The chordae tendineae and

Table I. Cardiac catheterization data

Location	Pressures (mm. Hg) Phasic	Mean	Oxygen saturation (%)
Pulmonary wedge		14	
Pulmonary artery	26/10	20	68
Right ventricle	31/2/6		67
Right atrium	8/2	4	67
Left ventricle apex	190/10/24		
Left ventricle below aortic valve	110/12/?6		
Aorta	116/66	96	96

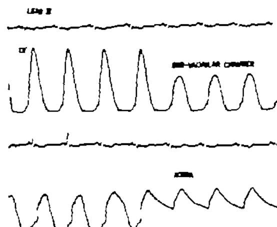


Fig. 1. Continuous catheter recording of pressures during withdrawal from apex of left ventricle to aorta. Note prominent atrial kick wave at beginning of ventricular pressure complexes.



Fig. Catheter in left ventricle. Arrow indicates cone-shaped subvalvular chamber. Deformed left ventricle is lower left; dye-filled left atrium is right. A second catheter is in pulmonary artery.



Fig. 3. Right atrium, tricuspid valve and right ventricle viewed from above. Fossa ovalis is at lower margin. Arrow indicates encroachment on right ventricle by hypertrophic left ventricular myocardium.

papillary muscles were normal, as were the posterior leaflet and the commissures. There were a few small, rounded nodules near the free margin of the anterior leaflet although some of these involved the atrial surface they were more conspicuous on the ventricular surface. The base of this leaflet was normal.

The size of the outflow tract of the left ventricle was diminished by a solitary protruding mass of hypertrophic muscle which was located at the junction of the membranous and muscular portions of the interventricular septum. The average thickness of this muscle was 2.8 cm., whereas that of the free wall of the left ventricle was 2.0 cm. (ratio of 1.4). The endocardium covering this area was opaque and lusterless and the thickness varied from 2 to 3 mm. Directly opposite the area of muscular hypertrophy the anterior leaflet of the mitral valve was taut (Fig. 4). The solitary mass of hypertrophic muscle and the anterior leaflet of the mitral valve were the principal boundaries of what amounted to a small, cone-shaped accessory chamber in the outflow tract of the left ventricle.

As viewed from above (Fig. 4), the aortic valve was normal, but the subaortic lesions could be seen when the leaflets were retracted. There were small atherosclerotic plaques midway between the free margins and the bases of two leaflets. The ventricular surface of all three aortic leaflets showed a moderate degree of thickening, which was regarded as being a jet lesion. The aortic commissures were normal, and the leaflets were pliable.

Microscopically the muscle fibers were hypertrophic and there was patchy interstitial fibrosis. The nuclei were dysplastic. The thickened endocardium consisted of dense collagen some of which appeared to be degenerating.

There were neither gross nor microscopic lesions which could be regarded as those of rheumatic endocarditis. The changes in the anterior mitral leaflet were thought to be the result of aging and/or jet lesions.

Discussion

Is IHSS congenital or acquired? Cases have been reported among the stillborn[4] and during the first year of life. In some instances there has been a familial occurrence. Brock's report of a patient with hypertension who developed IHSS seems most likely to be an example of an acquired form of the disease. In one series, the average age of the patients with IHSS was 25.7 years with the highest incidence in the third and fourth decades of life.[7] To our knowledge this report cites the oldest patient in whom detailed clinical and angiographic studies have been performed. There have been isolated reports of IHSS among people older than the age of 67 years but these are not well documented. Friedberg's textbook contains a photograph of a heart from a 67 year-old man with IHSS, but catheterization data are not given.

In this case the dynamic nature of IHSS with its transient changes in the severity of obstruction is quite apparent since the patient had had frequent, intermittent attacks of shortness of breath, dizziness, and syncope for several years. Exercises which tended to reduce the venous inflow to the heart such as squatting, stooping at the waist, or kneeling made his symptoms worse or initiated attacks of syncope. These symptoms are caused by a mechanism which is probably similar to that producing symptoms among patients with IHSS who



Fig. 4. Aortic valve from above. Fenestrations in cusps are normal. Arrow indicates hypertrophic, bulging subvalvular myocardium. To left of arrow is taut septal leaflet of mitral valve.

perform the Valsalva maneuver. Any technique which decreases cardiac venous inflow reduces the area of the left ventricular outflow tract and increases the obstruction to blood flow. Some reports have indicated that the administration of digitalis glycosides increases the systolic pressure gradient across the area of obstruction.[11] Whether digitalization of this patient caused worsening of his condition is speculative, but his condition did, in fact, become worse after the administration of digitalis.

Atrial fibrillation is an uncommon finding in IHSS and when present is of ominous portent.[12] The important contribution of atrial contraction to filling of the noncompliant left ventricle in IHSS is confirmed by the sudden worsening of the patient's condition during his paroxysms of atrial fibrillation. Mitral regurgitation frequently accompanies IHSS.[13] Distortion of the mitral valve leaflets or displacement of the valve attachments by hypertrophied muscle is considered to be the mechanism responsible for regurgitation.

Summary

The case of a 67 year-old man with idiopathic hypertrophic subaortic stenosis is presented. The diagnosis was made by clinical and laboratory methods, and was confirmed at necropsy. This report adds to the knowledge of the natural history of this dynamic cause of obstruction of the left ventricular outflow tract.

REFERENCES

1. Schmincke, A.: Über linkseitige muskulöse Conusstenosen, Deutsche med. Wchnschr. 33:2082, 1907.
2. Neufeld, H. N., Ongley, P. A., and Edwards, J. E.: Combined congenital subaortic stenosis and infundibular pulmonary stenosis, Brit. Heart J. 22:686, 1960.
3. Walther, R. J., Madoff, I. M., and Zinner, K.: Cardiomegaly of unknown cause occurring in a family. Report of three siblings and review of the literature, New England J. Med. 263:1104, 1960.
4. Livesay, W. R., Wagner, E. L., and Armbrust, C. A., Jr.: Functional subaortic stenosis due to cardiomyopathy of unknown origin, Am. Heart J. 60:935, 1960.
5. Daoud, G., Gallaher, M. E., and Kaplan, S.: Muscular subaortic stenosis, Am. J. Cardiol. 7:860, 1961.
6. Brock, R.: Functional obstruction of the left ventricle (acquired aortic subvalvular stenosis), Guy's Hosp. Rep. 106:221, 1957.
7. Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. G.: Idiopathic hypertrophic subaortic stenosis, Circulation 30: Suppl. No. 4, 116, 1964.
8. Fix, P., Moberg, A., Söderberg, H., and Karnell, J.: Muscular subvalvular aortic stenosis, Acta Radiol. Diag. 2:177, 1964.
9. Friedberg, C. K.: Diseases of the heart, ed. 2, Philadelphia, 1956, W. B. Saunders Co., p. 788.
10. Braunwald, E., Oldham, H. N., Jr., Ross, J., Jr., Linhart, J. W., Mason, D. T., and Fort, L., III: The circulatory response of patients with idiopathic hypertrophic subaortic stenosis to nitroglycerin and to the Valsalva maneuver, Circulation 29:422, 1964.
11. Braunwald, E., Brockenbrough, E. D., and Frye, R. L.: Studies on digitalis. V. Comparison of the effects of ouabain on left ventricular dynamics in valvular aortic stenosis and hypertrophic subaortic stenosis, Circulation 26:166, 1962.
12. Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. G.: Idiopathic hypertrophic subaortic stenosis, Circulation 30: Suppl. No. 4, 20, 1964.
13. Cohen, J., Effat, H., Goodwin, J. F., Oakley, C. M., and Steiner, R. E.: Hypertrophic obstructive cardiomyopathy, Brit. Heart J. 26:16, 1964.

Pulsus and electrical alternans due to the presence of a mitral caged ball-valve prosthesis

[illegible]

[illegible]

filling.

Case report

[illegible]

[illegible]

functioned well and the chest was closed. The post operatively course was uneventful, except for epi sode of trial flutter Conversion to sinus rhythm was spontaneous month later hile he was on digitalis. He was discharged on Coumadin nd 0.25 mg of digoxin daily nd was well except for mild fatigue He as no longer short of breath and his heart returned to normal size (Fig 1). His physicia discovered the presence of pulsus alternans in late 1965, and the alternans persisted over the next 2 months, through the time of this report. The pa tient ould not consent to second catheterization



Fig 1 Preoperative (*bov*) and 20 months post operatn (*below*) six-foot best films reveal redu tion in heart size los of the prominence f the left trial appendage nd the development of pleuropera hal dhesions. The Magovern vals is not seen in this reproduction.

Discussion

It has been known since 18, [2,3] that myocardial contractility may alter from beat to beat in the presence of a regular rhythm Thus, the definition of mechanical al ternans excludes bigeminy and the artifact which may be produced when the respira tory rate is one half of the pulse rate.[2] Sir Thomas Lewis[3] showed that mechanical alternation could exist in the atria, right ventricle or the left ventricle alone or in combination Left ventricular alternans usually means severe myocardial disease and consequently is associated with serious coronary disease aortic valve disease hy pertension or myocarditis [4] and alternans on the right side may coexist with the former or occur in cor pulmonale or certain congenital heart diseases. It has been rea soned that certain areas or certain fibers distributed throughout a sick heart might be unable to respond with each beat. This is consistent with the all or nothing law of Bowditch Although not disproving this theory other observations suggested that alternations in ventricular end-diastolic volumes might be responsible for mechan ical alternans After a premature beat, alternans may occur for a number of cycles, but again usually in a diseased heart The increased ejection fraction of the first post extrasystolic beat can leave such a small end-systolic volume that normal filling produces a subnormal end-diastolic vol ume and a weak contraction. The larger end-systolic volume of the weak beat plus diastolic filling would again lead to a strong beat Mechanical alternans has also been precipitated in some patients by phle botomy the erect posture or by tourni quets. Presumably such hearts need a high venous pressure to maintain high ven tricular end-diastolic stretch Here again the weak beat permits what would other wise be an inadequate venous return to aug ment the diastolic volume and give a trong contraction

Our patient with a slow rate of 60 per minute a normal blood pressure and al ternans would ordinarily be thought to have serious heart d sease and a poor prog nosis. [2] His heart size was normal The brachial arterial pressure recording (Fig 2) shows classic pulsus alternans. The respi ratory rate at the time was 14 per minute.



Fig 2 Apical phonocardiogram brachial intra-arterial pressure recording and simultaneous Lead V See text for explanation

The accompanying phonocardiogram reveals an absent opening snap after the strong contraction suggesting that the ball was prevented from hitting the cage in early diastole. Poor left ventricular filling would then lead to a high left atrial pressure and to the fourth sound which is seen preceding the weak beat. A primary discordant atrial alternans causing a strong atrial contraction to precede a weak ventricular contraction seems to be very unlikely The opening snap is clearly seen after the poor contraction Fig 3 shows a presystolic rumble after the fourth sound and a rumble following the opening snap namely at times when the left atrial pressure should be particularly high and the left ventricular pressure low The stronger beat shows a longer ejection period (0 28 second compared with 0 22 second)

Guntheroth and associates[13] thought that an occasional pulsus alternans can be due to a supernormal rather than a normal systole alternating with a weak systole. Potentiation however in causing supernormal beats usually decreases the ejection period [14] A supernormal beat is usually followed by an increased rate of relaxation [15] The ball would have been more likely to hit the cage after the strong systole had the strong beats in our case been due to potentiation The Q-P_2 interval remained constant, suggesting that right ventricular alternans was not present,[16] but the A_2 occurred earlier in the weak beats, causing alternate splitting of S_2

As in most cases of mechanical alternans, the P I intervals are not absolutely regular Measurements show that the P wave of the weak beat is 0 01 second early Such a brief shortening of late diastole is insufficient to cause the pulsus alternans. It is postulated that either increased mechanical traction on the atrium during strong ventricular systole accelerates the atrial pacemaker[18] or the higher pressure resulting from the strong systole reflexly causes atrial slowing The reflex takes time and slows the heart after the weak beat.

Electrical alternans is less common than mechanical but was noticed in subtle form on the electrocardiogram of this patient and was more clearly seen on the scrolled vectorcardiogram (Fig 4) Bertrand and associates[20] suggested that the electrical alternans may be more often present that has been thought, since he has demonstrated it by intracardiac electrocardiograms when it was not present on standard leads It would be tempting to think that impingement of the caged ball-valve on the left ventricular septum of our patient might disturb the electrical activity of the heart.

It seems to be unlikely that alternate conduction pathways would be refractory during every other beat because of serious intrinsic heart disease in our patient. The difference between the vectorcardiographic forms of the two types of systole are such that one cannot be considered to be a linear transformation of the other This would indicate that the differences are not due to a change in cardiac position within the volume conductor from beat to beat.[21]

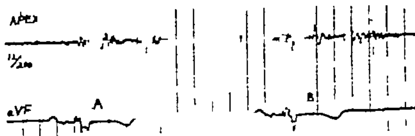


Fig 3 Apical phonocardiogram recorded in the 20 to 200 frequency band with paper time lines 0 1 second apart and Lead VF See text for explanation.

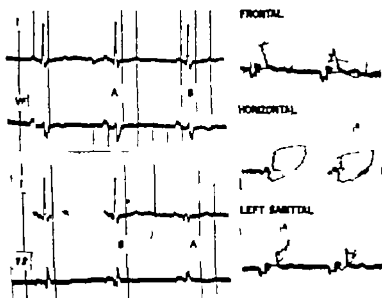


Fig 4 Leads I V and V and tetrahedron ectorcardiograms scrolled t 50 mm. per second on the X xis of the frontal and horizontal planes and on the Z axis of the left sagittal plane A corresponds to the mechanically tronger beat nd B to the weaker beat.

It is well established that prosthetic valves in the mitral position do not offer a normal sized diastolic orifice and small gradients are found across these valves at rest and higher gradients are found with exercise.[22] Beck[23] found the highest gradient among his patients in one with aortic valve disease and a greatly hypertrophied left ventricle. He thought that the hypertrophied septum interfered with the function of the prosthetic mitral valve. The fact that alternans did not appear in our patient until the heart had become smaller plus the above-mentioned findings, make t very likely that the tronger contraction and more complete chamber empty ng caused poor ball movement poor ventricular filling and a weak alternate beat. That this has not been reported before may be related to the positioning of the prosthesis in the chamber It may also be related to a certain critical reduction in the ejection fraction with the weak contractions permitting free movement of the ball with alternate beats.

Summary

Almost 2 years after a successful mitral val e replacement with a ball alve prosthesis a 54-year-old patient was found to have mecha ical and electrical alternans. E idence is presented to suggest that strong l ft ventricular contraction and therefore, a small early diastol chamber

size can interfere with the functioning of the ball valve and produce pulsus alternans. This is the first report of such a case.

REFERENCES

1. Traube, L. Ein Fall von Pulsus Bigeminus, Berlin. Klin. Wchnschr. 9:185, 1872.
2. Bellet, S. Clinical disorders of the heart beat, ed. 2, Philadelphia, 1963, Lea & Febiger, p. 551.
3. Lewis, T. The mechanism and graphic registration of the heart beat, ed. 3, London, 1925, Shaw and Sons, Ltd.
4. Thompson, W. P., and Levine, S. A. Pulsus alternans, Am. Heart J. 11:135, 1936.
5. White, P. D. Failure of the left ventricle without failure of the right ventricle, J.A.M.A. 100:1993, 1933.
6. Gaskell, W. H. Rhythm of heart of frog and nature of action of vagus nerve, Phil. Tr. Roy. Soc. 173:993, 1882.
7. Mines, G. R. On dynamic equilibrium in the heart, J. Physiol. 46:349, 1913.
8. Marshall, J. H., Sarnoff, S. J., and Sonnenblick, E. H. The dynamics of pulsus alternans: Alternating end-diastolic fiber length as a causative factor, J. Clin. Invest. 42:55, 1963.
9. Wenckebach, K. F. Zur Analyse des unregelmässigen Pulses. 4. Über den Pulsus Alternans, Ztschr. klin. Med. 44:218, 1901.
10. McIntosh, H. D. Discordant pulsus alternans, Circulation 21:214, 1960.
11. White, P. D. Heart disease, New York, 1931, The Macmillan Co., p. 596.
12. Windle, J. D. Pulsus alternans, Quart. J. Med. 6:453, 1913.
13. Guntheroth, W. G., Morgan, B. C., Lintermans, J. P., McGough, G. A., and Figley, M. M. Supernormal character of the strong beat in pulsus alternans, Circulation 32: Suppl. 2, p. 104, 1965.
14. Braunwald, E., Ross, J., Jr., Sonnenblick, E. H., Frommer, P. L., Braunwald, N. S., and Morrow, A. G. Slowing of heart rate, electroaugmentation of ventricular performance and increase in myocardial oxygen consumption produced by paired electrical stimulation, Bull. New York Acad. Med. 41:481, 1965.
15. Hoffman, B. F., Bartelstone, H. J., Scherlag, B. J., and Cranefield, P. F. Effect of postextrasystolic potentiation on normal and failing hearts, Bull. New York Acad. Med. 41:498, 1965.
16. Ferrer, M. I., Harvey, R. M., Cournand, A., and Richards, D. W. Cardiocirculatory studies in pulsus alternans of the systemic and pulmonary circulation, Circulation 14:163, 1956.
17. Friedman, B. Alternation of cycle length in pulsus alternans, Am. Heart J. 51:701, 1956.
18. Scherf, D., Scharf, M. M., and Goklen, M. F. Effect of stretch and pressure on stimulus formation in the dog's auricle, Proc. Soc. Exper. Biol. & Med. 70:708, 1949.
19. Hogancamp, C. E., Kardesch, M., Danforth, W. H., and Bing, R. J. Transmembrane electrical potentials in ventricular tachycardia and fibrillation, Am. Heart J. 57:214, 1959.
20. Bertrand, C. A., Zohman, L. R., and Williams, M. H. Intracardiac electrocardiography in man, Am. J. Med. 26:534, 1959.
21. Brody, J. G., and Rossman, P. L. Electrical alternans, J.A.M.A. 108:799, 1937.
22. Schaffer, A. I. The body as a volume conductor in electrocardiography, Am. Heart J. 51:588, 1955.
23. Littman, D., and Spodick, D. H. Total electrical alternans in pericardial disease, Circulation 17:912, 1958.
24. Morrow, A. G., Clark, W. D., Harrison, D. C., and Braunwald, E. Prosthetic replacement of the mitral valve, Circulation 29: Suppl. 2, 1964.
25. Beck, W., Ferguson, D. J. G., Barnard, C. N., and Schrire, V. Hemodynamic findings following replacement of the mitral valve with the University of Cape Town prosthesis, Circulation 32:721, 1965.

Diagnosis of left superior vena cava by clinical inspection, a new physical sign

Arnold L. Colman, M.D.
San Francisco, Calif.

Recent technical advances in cardiovascular surgery have provided a greater impetus to the development of sophisticated laboratory diagnostic methods. Cardiac catheterization, phonocardiography, vectorcardiography, and angiography have thus allowed the relatively precise diagnosis of various congenital and acquired cardiovascular lesions. Similarly the availability of surgical cures for formerly hopeless anomalies has brought about the more critical application of basic methods of physical diagnosis, since it is through these methods, plus routine roentgenography, that candidates for more advanced study are found.

To my knowledge the following is the first reported case in which a left superior vena cava was diagnosed on clinical examination and subsequently confirmed by angiography.

Case report

A 23-year-old white man gave a history of cyanosis and digital clubbing since infancy. Frequent squatting, dyspnea on exertion, and a cardiac murmur led to the diagnosis of tetralogy of Fallot in childhood.

In September 1965 studies undertaken at another institution because of vertigo, diplopia, nausea, and vomiting of undetermined etiology revealed multiple congenital anomalies, including right-sided aortic arch, intracranial arteriovenous malformation, extensive bronchial and pulmonary arterial collateral circulation to the lungs, and malrotation of the jejunum.

Physical examination on Oct. 7, 1965, revealed a tall (6 feet 1 inch), thin (130 pounds), cyanotic male with marked clubbing of the long slender digits. The pulse was regular at 80 per minute. The blood pressure was 115/80 mm. Hg in both arms. Inspection of the head revealed atresia of the left external auditory canal, with absence of the pinna, and prognathism. Horizontal and vertical phasic nystagmus was present. The palate was high and arched. Examination of the neck with the patient reclining at 30 degrees revealed exaggerated pulsations with dominant palpable a waves in the left internal jugular vein. Auscultation over the left jugular bulb revealed a presystolic sound synchronous with the large a wave, immediately preceding the carotid pulse. This sound was followed, after a brief interval, by a long systolic murmur. There was no visible jugular pulse on the right side, nor was there external jugular venous distention on either side. The chest was asymmetrical with a large precordial bulge. The lungs were clear. There was a faint thrill along the left sternal border and a slight right ventricular parasternal lift. An apical impulse was felt in the left anterior axillary line. The second heart sound was single and accentuated at the pulmonic area. A Grade 4/6 long systolic murmur was heard loudest in the third left intercostal space with radiation to the left axilla and the neck. No diastolic murmur was heard, nor was there a fourth heart sound corresponding to the presystolic left internal jugular sound. The peripheral pulses were full and equal, without bruit or femoral delay. The abdomen and genitalia were normal. Neurologic examination revealed mild truncal ataxia and marked ataxia of the upper extremities. Muscle strength was normal in the arms, but there was minimal weakness in the legs, with hyperactive tendon reflexes and Babinski

Received for publication Feb. 21, 1966.

*Clinical Instructor in Medicine, University of California School of Medicine; Attending Physician, Laguna Honda Hospital and Rehabilitation Center; Adjunct in Medicine, Mount Zion Hospital and Medical Center, 450 Sutter St., San Francisco, Calif.

lgns bilateral. The sensory examination was negative.

Laboratory studies revealed hemoglobin of 17.6 Gm. per 100 ml. and hematocrit of 50 per cent. White blood cell and differential counts and urinalysis were normal. An electrocardiogram showed a normal rhythm at rate of 3 per minute. The axis was indeterminate with biphasic complexes in the extremity leads. Tall R waves (28 mm. in Lead V) and inverted T waves were present in Leads V . Tracings of the jugular venous pulse were taken at the bedside using simple photoelectric method previously described (Fig. 1).

On Oct. 28, 1963 percutaneous angiography was performed via the left antecubital vein with injection of 40 ml. of 60 per cent Renografin in an effort to demonstrate the left superior vena cava (Figs. 2 and 3).

Subsequent to these studies data obtained at cardiac catheterization at another hospital in August 1964 became available. The catheter had been introduced into the right atrium from the right arm presumably via right superior vena cava. The essential findings were a large right-to-left shunt at the ventricular level and a large systolic gradient across the pulmonary valve (RV pressure 115/15, PA pressure 16/12, and RA mean pressure 10 mm. Hg).

On Nov. 23, 1965 the patient sustained a profound left hemiplegia. He rapidly became comatose and died on November 30. Pertinent findings at autopsy* included a 3-cm. interventricular septal defect, dextroposition of the aorta, severe pulmonary stenosis, and right ventricular hypertrophy. The orifice of the (right) superior vena cava was markedly stenotic, barely admitting the tip of the little finger. A large, thin-walled left superior vena cava, identified only after deliberate search, entered the right atrium via the coronary sinus, which was greatly dilated. The cause of death was thrombosis of a vascular malformation involving the medulla and superior spinal cord, with aspiration bronchopneumonia.

Discussion

Embryology. The cephalic half of the early embryo is drained by the right and

*Performed by Dr. R. Boar.

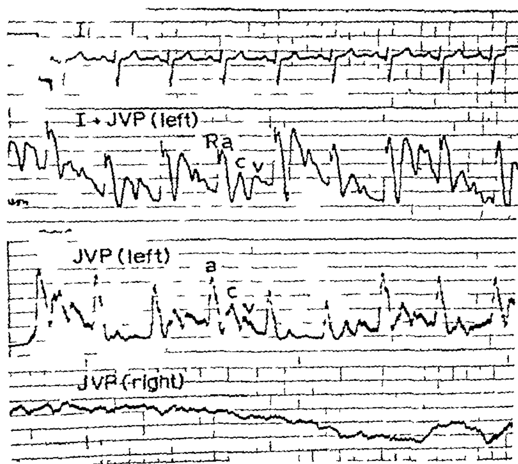


Fig. 1. *Top.* Lead I ECG. *Second strip.* Combined lead I ECG and jugular pulse tracing recorded from the left jugular bulb region. The R wave of the ECG permits identification of the venous waves. *Third strip.* Left jugular pulse tracing alone. A dominant a wave is clearly shown. *Bottom.* Tracing recorded from the right jugular vein. Distinct venous pulse waves are absent.



Fig 2 Venous angiogram showing well-developed left superior vena cava The catheter was introduced via the left antecubital vein.



Fig 3 Catheter advanced from the position shown in Fig 2 into the left superior vena cava.

left anterior cardinal veins each of which joins the corresponding posterior cardinal vein to form the right and left common cardinal veins (ducts of Cuvier) (Fig 4) The common cardinal veins enter the sinus venosus at the caudal end of the primitive tubular heart. The cephalic, or distal portions of the two anterior cardinal veins remain in adult life as the internal jugular veins. The proximal portion of the right anterior and common cardinal veins persists as the superior vena cava but with the development of a cross channel (the future left innominate vein) shunting blood from the left to the right anterior cardinal vein the proximal portion of the left anterior cardinal vein normally disappears. The left common cardinal vein remains as the coronary sinus.[1]

Infrequently (0 28 per cent of autopsies) the proximal left anterior cardinal vein does not disappear but persists as a left superior vena cava (LSVC) The developmental history of this vessel explains why it commonly drains into the coronary sinus with no resulting hemodynamic derangement since the venous blood is duly returned to the right atrium In a few cases the LSVC drains into the left atrium producing a right-to-left shunt. Usually the persistent LSVC is accompanied by its normal right counterpart, but in some cases the right SVC is reduced in size or

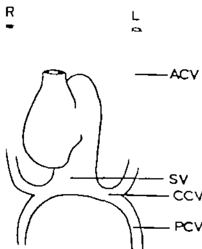


Fig 4 Great veins in the early embryo *ACV* Anterior cardinal vein. *SV* Sinus venosus *CCV* Common cardinal vein. *PCV* Posterior cardinal vein.

may be replaced by an atretic remnant in which case the LSVC is the major vessel draining the upper half of the body. Absence of the right SVC has been reported in only 30 cases. When the LSVC persists, the left innominate vein is often absent.

Significance of LSVC. LSVC has been found in 3 to 4 per cent of patients investigated for congenital heart lesions.[7] Gensini and associates[4] found atrial septal defect with anomalous pulmonary venous drainage to be the most common associated congenital heart lesion but Wood[8] found a LSVC always with a RSVC as well in 20 per cent of patients with tetralogy of Fallot. Conversely tetralogy was present in over 50 per cent of Wood's patients in whom a LSVC persisted.

Excluding those cases in which there is anomalous drainage of the LSVC into the left side of the heart or anomalous pulmonary venous drainage into the LSVC, the clinical significance of the LSVC is that of the associated anomalies. However when cardiac catheterization is performed the presence of a LSVC assumes greater importance. When the right atrium is entered via the LSVC and coronary sinus it is very unlikely that the catheter will pass easily through the right ventricle to the pulmonary artery since the direction of the catheter emerging from the coronary sinus is unfavorable. More important, catheterization of the coronary sinus has been associated with chest pain collapse and electrocardiographic changes consistent with myocardial ischemia,[9] and at least one instance of fatal cardiorespiratory arrest has resulted from excessive vagal stimulation due to attempts to manipulate the catheter into the LSVC.[10] Moreover in one series the incidence of supraventricular tachycardia during catheterization was 38 per cent in patients with LSVC compared to 7.9 per cent in patients with only the right SVC.

Most important is the potential surgical significance of a LSVC during open-heart procedures. As Gensini and associates[4] have stated discovery of the LSVC prior to surgery indicates certain technical procedures necessary to prevent disastrous results. The anomalous vessel must be either occluded or cannulated when cardiopulmonary bypass or hypothermia is used in order to prevent excessive loss of blood and poor visualization. Cooley and associates suggested that the LSVC be occluded within the pericardium so that the venous return via the hemiazygous vein can also be controlled. Gensini's group[4] utilized a special balloon tipped catheter introduced and inflated in the coronary sinus to arrest the flow from the LSVC. The presence of the LSVC may also require a modification of the intended procedure, depending on whether it terminates in the right or left atrium and whether it receives anomalous pulmonary veins.[11]

Diagnosis of LSVC. As recently as 1951 it was stated that LSVC was rarely diagnosed during life.[12] Since then the diagnosis has been made with increasing frequency (usually as an incidental finding) during cardiac catheterization angiocardiography or surgery. Unfortunately none of these methods will unfailingly reveal the LSVC.

Various authors[4-7,14] have stated that the diagnosis of LSVC by cardiac catheterization is unreliable since the anomalous vessel is often not discovered when the approach is via the right arm. Similarly angiography in the not infrequent cases without a cross communication between the two superior venae cavae, will reveal the LSVC only if the injection is given into the left arm.[11] For this reason Árvay and Álmos stress that angiography should always be performed via both arms in cases of congenital heart disease since the approach via the right arm is also required to assess the condition of the right SVC.

In plain roentgenograms, widening of the vascular pedicle may be seen in some but by no means in the majority of cases of LSVC.[8] A crescentic shadow representing the LSVC was found (retrospectively) between the aortic arch and the middle third of the clavicle in 15 of 30 cases.[7]

Even surgical exploration is not an infallible means of revealing the LSVC, particularly if a median sternotomy approach is used since the surgeon cannot visualize the extrapericardial portion of the vessel. Since the intrapericardial portion is on the posterior aspect of the heart it can be viewed only by lifting the apex of the heart out of the pericardial sac. This maneuver may produce arrhythmias and/or hypotension due to angulation of the veins, but

has been considered to be imperative since an undetected LSVC may endanger the life of the patient.[8]

Because an *unsuspected* LSVC can be missed by all methods of examination any clue to its existence becomes important. Although Campbell and Deuchar[14] summarized current opinion when they wrote that "there are no clinical signs or symptoms to suggest the presence of a left-sided superior vena cava the diagnosis in the present case was strongly suspected on the basis of simple inspection of the neck.[11] Normally the jugular pulse is more prominent on the right side since the right internal jugular vein right innominate vein, and right superior vena cava form a relatively straight communication with the right atrium whereas the left internal jugular vein communicates with the right SVC via the longer and nearly horizontal left innominate vein (Fig 5) In this patient, the lack of significant pulsation in the right internal jugular vein in the absence of evidence of obstruction of the right venous system i.e. cervical venous engorgement, and in the face of excessive pulsation of the left internal jugular vein, was thought to be explicable only by the presence of a LSVC, and a diminished or absent right SVC In fact, the right SVC was present, but its stenotic orifice precluded significant venous pulsation although it admitted the cardiac catheter

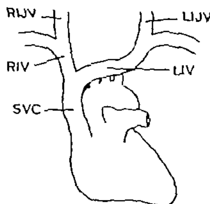


Fig 5 Great veins in the adult. *RIJV* Right internal jugular vein. *LIJV* Left internal jugular vein. *RIV* Right innominate vein. *LIV* Left innominate vein. *SVC* Superior vena cava. Note the nearly right angle between the left innominate vein and the superior vena cava

Another possible explanation of the prominent left-sided venous pulse is the fact that the coronary sinus forms part of the posterior wall of the heart. It is thus conceivable that pulsations may be transmitted to the left jugular system either via direct impact of left atrial contractions on the coronary sinus portion of the LSVC or by active participation of the wall of the coronary sinus in atrial systole, acting as a pump forcing blood back into the veins.

It seems to be more likely however that the dominant left jugular *a* wave and its auscultatory counterpart, the presystolic jugular sound[14] are manifestations of increased right heart pressure due in this case to pulmonic stenosis. It is true that giant *a* waves are uncommon in tetralogy of Fallot, because of the presence of the ventricular septal defect. According to Wood[8] however dominant *a* waves are seen in 20 per cent of cases. Moreover in pulmonic stenosis with reversed interatrial or interventricular shunt (the latter resembling tetralogy except for the lack of overriding of the aorta) giant *a* waves were found in 60 per cent, and smaller but still dominant *a* waves in 26 per cent.

The presystolic sound heard over the left jugular bulb resembled acoustically a normal heart sound although no sound of similar timing was heard over the heart itself It was apparent that the three synchronous observations—*visible* venous wave *palpable* venous pulsation and *audible* venous vibration—all occurring immediately preceding the carotid pulse, were manifestations of a single event, viz forceful regurgitation of blood into the vein with atrial systole. Dock[3] has described presystolic jugular sounds as a sign of right atrial hypertension. Earlier Mackenzie[3] had attributed this finding to tensing of the valves above the inferior jugular bulb due to forceful venous pulsations. Similar sounds have frequently been observed in normal individuals in association with the usual respiratory augmentation of the *a* wave.[13]

It would seem to be likely that this physical sign will prove to have a high degree of specificity The only condition which might cause confusion is distention of the left jugular veins sometimes seen as a result of compression of the

vein behind the sternum by a sclerotic, unfolded aortic arch. In most such instances, fixed distention of the left external jugular vein is present.[16] In some cases, however, pulsation of the internal jugular vein at a higher level in the neck has been noted.[1] The essentially obstructive nature of this phenomenon may be revealed by noting the effect of deep inspiration which causes the distended vein to collapse. The pressure then rises during expiration by a series of systolic "kicks."[1] Further evidence of unfolding of the aorta may be found in marked arterial pulsations due to kinking of the right carotid and innominate arteries usually seen in elderly women and frequently mistaken for carotid or innominate aneurysms.

Like most physical signs, the paradoxical jugular pulse must be looked for to be appreciated. The sensitivity of the sign determined by the number of false negatives remains to be shown by accumulated experience. It is hoped that attention to the jugular pulse will at least yield an awareness of the possible existence of a LSVC in patients with congenital heart disease so that steps may be taken to make a definitive diagnosis of this potentially important anomaly.

Summary

A case is presented of a patient with probable Marfan's syndrome and multiple congenital anomalies, including tetralogy of Fallot with a persistent left superior vena cava.

The embryonic origin of the superior vena caval system is briefly reviewed and the left superior vena cava is discussed with respect to its clinical and surgical importance and methods of diagnosis.

A physical sign of left superior vena cava is described. It consists of jugular venous pulsations more marked on the left side in the absence of evidence pointing to obstruction of the right innominate or jugular veins or compression of the left innominate vein by an arteriosclerotic aortic arch.

This simple clinical clue may alert the physician to the possible existence of an anomaly which can be a serious hazard in patients undergoing open heart surgery for congenital defects.

I am indebted to Dr. A. Stone and Dr. S. Sunseri for permission to report this case. Angiography was performed by Dr. M. Thoshinsky.

REFERENCES

1. Colman, A. L.: A simplified method of recording the jugular venous pulse, Am. Heart J. 70:160, 1965.
2. Patten, B. M.: Human embryology, Philadelphia, 1946, Blakiston.
3. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Co.
4. Karnegis, J. N., Wang, Y., Winchell, P., and Edwards, J. E.: Persistent left superior vena cava, fibrous remnant of the right superior vena cava and ventricular septal defect, Am. J. Cardiol. 11:573, 1963.
5. Gensini, G. G., Caldini, P., Casaccio, F., and Blount, S. G.: Persistent left superior vena cava, Am. J. Cardiol. 4:677, 1959.
6. Arvay, A., and Almos, S.: Diagnosis and surgical significance of left-sided vena cava superior, Acta Chir. Acad. Sci. Hung. 3:303, 1962.
7. Fraser, R. S., Dvorkin, J., Rossall, R. E., and Eidem, R.: Left superior vena cava. A review of associated congenital heart lesions, catheterization data and roentgenologic findings, Am. J. Med. 31:711, 1961.
8. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1956, J. B. Lippincott Co.
9. McMichael, J., and Mounsey, J. P. D.: A complication following coronary sinus and cardiac vein catheterization in man, Brit. Heart J. 13:397, 1951.
10. Haeger, K., Juhlin, I., and Krook, H.: Eisenmenger's complex accompanied by double superior venae cavae, the left draining into the left atrium. Report of a case with fatal outcome due to vagus irritation during heart catheterization, Am. Heart J. 50:171, 1955.
11. Cooley, D. A., Latson, J. R., and Keats, A. S.: Surgical considerations in repair of ventricular and atrial septal defects utilizing cardiopulmonary bypass, Surgery 43:214, 1958.
12. Hurwitt, E. S.: The surgical importance of persistent left superior vena cava, Arch. Dis. Childhood 34:1, 1959.
13. DeGroot, J. W. C.: Bilateral superior venae cavae accompanied by patent ductus arteriosus, Brit. Heart J. 13:403, 1951.
14. Campbell, M., and Deuchar, D. C.: The left-sided superior vena cava, Brit. Heart J. 16:423, 1954.
15. Colman, A. L.: Clinical examination of the jugular venous pulse, Springfield, Ill., 1966, Charles C Thomas.
16. Dock, W.: Loud presystolic sound over the jugular veins associated with high venous pressure, Am. J. Med. 20:853, 1956.
17. Mackenzie, J.: Diseases of the heart, ed. 3, London, 1914, Oxford University Press.
18. Shirley Smith, K.: The kinked innominate vein, Brit. Heart J. 22:110, 1960.
19. Sleight, P.: Unilateral elevation of the internal jugular pulse, Brit. Heart J. 24:726, 1962.

Review

Vascular reactivity in essential and renal hypertension in man

Milton Mendlowitz, M.D.
New York, N. Y.

Vascular reactivity in animals, with hypertension produced by a variety of techniques, is a new and confused subject with a paucity of experimental observations. One can cite, among others, the increased l-norepinephrine (NE) pressor responsiveness of hereditary hypertension in rats even before the administration of salt elicits the elevation in blood pressure and the curious decrease in responsiveness to angiotensin II (AT) in the contralateral kidney of dogs when unilateral renal ischemia is produced. In the present state of our knowledge, however, it is difficult to ascertain to what extent observations in this field in animals can be extrapolated to throw light on mechanisms in essential, renal, or other varieties of hypertension in man. Therefore, it seems to be best to confine this discussion to *human* vascular reactivity with particular reference to renal hypertension.

Vascular reactivity in man has been tested under many circumstances and by different procedures in normotensive subjects as well as in patients with different diseases, including various hypertensive states. The test substances used have included epinephrine, NE, AT[3] and tyramine as well as depressor drugs such as hexamethonium[7] and phentolamine. Various vascular beds have been studied including those of digital skin,[4] forearm muscle[11,12] and skin,[13] thigh muscle, kidney,[13] lung,[14] and brain,[17] as well as the systemic circulation as a whole.[4] Some of these studies have tested pressure responses alone[10,22] whereas others have tested pressure and flow together.[4,10,23] Different methods have been used to measure pressure and flow, and controversy has developed with reference to the interpretation of the results, particularly as to changes in "peripheral resistance."[23,27] In some instances, moreover, single doses of the test substances were administered and the peak effects recorded[10,22] whereas in others, either intravenous or intra-arterial infusions were employed and the changes per unit of test substance infused per minute were recorded for each steady state.[10-1,23,2,23] The control steady state in some studies consisted merely of recumbency of the subject in a quiet room with or without any attempt to control ambient temperature.[11,23] In other investigations, postural effects because of varying degrees of uprightness color the results, particularly of the effects of depressor drugs.[27] In still other studies, the control and pressor test observations were made after the administration of depressor drugs together with, or at times without,[12] indirect or direct heating.

In addition to these relatively direct observations, some investigators have studied

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
Aided by Grant HE-04446 (CV) from the National Heart Institute, United States Public Health Service.
Received for publication June 20, 1966.
Address: The Mount Sinai Hospital, 0th St. and Fifth Ave., New York, N. Y. 10029.

the effect of exercise[20,21] and of mental strain[22] on the circulation whereas others have studied critical closing or opening pressure[23-26] and have drawn inferences in regard to reactivity and vasomotor tone in hypertensive states.

Most of this work has concerned itself with essential rather than renal hypertension and may be summarized as follows The weight of the evidence indicates that there is increased systemic vascular reactivity in essential hypertension[1-27] This seems to be demonstrated best if both pressure and flow are measured together preferably after at least partial inhibition of reflex effects by ganglion blockade or indirect heat or both[27] Infusion is preferable to single injection in this regard and intra arterial infusion has the advantage of minimizing general baroreceptor and other responses affecting the regional circulation measured[27] Increased reactivity is also more easily demonstrated in vascular beds under the strongest sympathetic nervous control such as the arteriovenous anastomoses of the digit.[27] Normal vascular reactivity in essential hypertension has been reported for the kidney[14] the systemic blood pressure,[21] and for the systemic resistance in one study[14] but in each of these investigations either single injections or intravenous rather than intra arterial infusions were given and no attempt was made at preliminary blockade of reflex moderator mechanisms. There is also increased neural vasoconstriction in hypertension which can be demonstrated by measuring flow and pressure before and after indirect heating supplemented by ganglion blockade a kind of negative reactivity[23,24] In the retina however vascular constrictive reactivity to the inhalation of 100 per cent oxygen has been found to be less than normal in essential hypertension.[24a]

Another difficulty in this type of investigation arises in the interpretation of the experimental results. If peripheral resistance, which is fundamentally a pressure-flow ratio is measured the factors in essential hypertension of change in critical closing pressure increase in intravascular distending pressure as well as of increased intrinsic narrowing of the vascular bed are disregarded[23] These factors do not necessarily cancel one another out and their neglect cannot be replaced by only measuring changes in resistance as a percentage of the initial resistance a maneuver which often buries existing real differences. One may add to this the difference between patients with essential hypertension and normotensive subjects with changes in posture[23,25] when studies are not performed with the subjects in the recumbent position. Also some of the increase in reactivity in essential hypertension has been attributed to the hypertrophy of vascular smooth muscle which is known to exist in the disease,[23,24,41] rather than to any more specific biochemical or physiologic effects. Evidence against this may be adduced from the normal reactivity observed in Raynaud's disease[27] and in renal hypertension[27] despite hypertrophy and other changes in the vessels.

It should be noted that several observers have found increased reactivity to psychic stimuli as well as to exercise in essential hypertension and have inferred from this that essential hypertension represents increased cerebral excitability[22] or a state of increased readiness for effort.[34] This reasoning however is not yet on firm ground and thus far psychometric tests in the disease have not shown any differences from the normal.[42]

In more direct observations on peripheral blood vessels, one observer has demonstrated increased digital capillary narrowing when NF was infused into hypertensive subjects.[43] Others have observed increased responsiveness of conjunctival vessels to directly applied epinephrine in essential hypertension[44] and still other workers have found the critical closing or opening pressure to be higher than normal in essential hypertension[23-26,45] There has been some difference of opinion as to whether after reflex vasodilatation the critical closing or *opening pressure still remains increased* in the hypertensive patient.[1,23,46] If this were so it might imply the presence of a circulating vasoconstrictor Recently however it has been shown that it is possible to reduce critical closing or opening pressure to normal levels in essential hypertension after vasodilatation provided that direct as well as indirect heat is employed[46] The AT skin test[47] was originally reported to be positive in essential hypertension but has since been

shown by many observers to be no different from normal. The negativity of the results has some theoretical importance, since the chief vessels involved are probably the pre capillary sphincters.

It should be emphasized that there seems to be little difference between responses to the different vasoconstrictive agents, including NE, epinephrine, tyramine, and AT, except for large differences in dosage requirements.[27] Weight for weight, AT is ten times more potent than NE, which is more potent than epinephrine, and one hundred times more potent than tyramine.[15] The difference in response between normotensive and essential hypertensive groups, however, is the same regardless of the nature of the chemical stimulus and is always greater for essential hypertension.[27] This response can be modified by steroids[1,38] and by catecholamine-depleting[31] as well as by sodium-depleting drugs[32,33] sometimes differently in normotensive than in hypertensive groups. Thus, glucocorticosteroids increase reactivity in the normotensive and not in the hypertensive group whereas aldosterone and salt increase reactivity in the hypertensive group and only slightly in the normotensive group.[38] Guanethidine and alpha-methyldopa increase reactivity in patients with essential hypertension and chlorothiazide decreases such reactivity in the hypertensive patient and increases or decreases responsiveness in the normotensive subject depending on the vascular bed studied.[27,32,33,3]

Let us now confine the discussion to renal hypertension in man. These cases are not so easy to define as might appear at first glance. Moreover, it is questionable whether all renal hypertension in man is activated by the same or similar mechanisms.[35] For example, it is known that in acute glomerulonephritis, the hypertension is caused largely by an increase in blood volume[36] and cardiac output,[37] with little if any measurable change in peripheral resistance, whereas in chronic renal hypertension, as in chronic glomerulonephritis or renovascular hypertension, it is largely peripheral resistance which is increased. The chronic cases, particularly, must be carefully selected to exclude complicating essential hypertension.[37] Normal blood pressure prior to the onset of the disease and a negative family history of hypertension are of help, but unless a specific test identifying essential hypertension becomes available, it is always possible for mixed cases to creep into the renal hypertensive group.

It was first demonstrated by our group that, in the digit, provided that cases are carefully selected, reactivity to both NE[27,39] and AT[27,39] in renal hypertension is either within the normal range or only slightly elevated, in contrast to the marked increase over the normal in patients with essential hypertension.[2] Sympathetic neural discharge was inhibited and pressure together with flow were measured in these studies, and the factors of critical closing pressures, change in intravascular pressure and change in venous pressure were taken into account in the calculations by expressing the result in terms of work of vasoconstriction per microgram of NE or AT infused per minute.[22]

Later, another group of workers[40,41] introduced a test based on only a rise in brachial arterial blood pressure with infusion of AT. This test purported to distinguish renovascular from essential hypertension with the exception of accelerated hypertension. It was theorized that the renovascular and accelerated cases would be less responsive because the vessels were already being stimulated by circulating AT. It could be predicted on several grounds that difficulties would be encountered here. In the first place, no effort was made to counteract moderator and other reflexes by ganglionic blockade or other types of inhibition of the sympathetic nervous system. Also, it is known that, particularly in accelerated hypertension, cardiac output may be decreased and it is possible that flow in such cases may decrease more than normally with infusion of AT, making hazardous the interpretation of changes in pressure as an index of vasoconstriction. In nonaccelerated essential hypertension, however, Tuckman and associates have found the changes in cardiac output with infusion of NE to be no different from normal on the average, although the correlation with changes in pressure in individual cases was not good. The reasoning with respect to the specificity of an AT test in contrast to an NE test also falls down on the grounds that

reactivity to both substances was shown previously to be increased in essential hypertension and relatively normal in various types of renal hypertension when properly studied.[77] Moreover, evidence from radioactive tracer studies suggest a greater than normal store of AT[62, 63] and a less than normal store of NE[64, 65] in essential hypertension, thus making it difficult to reconcile changes in reactivity with changes in the amounts of these substances in the body.

Subsequent events have borne out the inadequacies of this test, which might a priori have been expected. Several workers[44] have failed to confirm its validity as a screening test for renovascular hypertension and have also found no correlation between levels of serum angiotensin or renin and pressor reactivity. In answer to their critics, the original authors of the test published a paper[4] in which good correlation was found between (1) their AT pressor sensitivity test, (2) a nonspecific test for pressor substance in renal vein blood,[3] and (3) successful surgical correction of the renovascular hypertension. The authors of (2) the renal pressor substance test, however, have not been able to demonstrate that this substance is either AT or renin. Yet the substance used in the pressor sensitivity test is AT. Moreover, in their most recent report, the authors of the latter test imply that patients with parenchymatous renal hypertension have a responsiveness similar to that of those with essential hypertension, an observation at variance with the findings of others.[77] All this, therefore, requires confirmation in the light of past experience, although it is possible that decreased pressor sensitivity with some overlap may be more indicative of renal than of essential hypertension.

The AT skin test,[77] when originally introduced, was also deemed to be positive in essential hypertension on the basis of reasoning similar to that of the authors of the AT infusion pressor test.[9] It was thought that essential hypertension was renal in origin and productive of increased endogenous AT, disregarding all observations to the contrary,[71, 73] and that the increased response to exogenous AT was related to this in some ill-defined way. The test would therefore, presumably, be even more positive in renal or renovascular hypertension. Three different groups of workers have since failed to confirm this work and have found no difference between hypertensive and normotensive subjects with respect to the response of the skin blood vessels to intradermal AT.[7, 7] In fact, it is now generally accepted that the response of these blood vessels to AT, although constrictive, is nonspecific and no greater in hypertensive than in normotensive subjects.

One may ask why differences should be found in infusion experiments and not after intradermal injection. The vessels affected by the AT skin test are probably chiefly precapillary sphincters which are not innervated by sympathetic nerves. Although these vessels can be constricted by locally injected or by circulating AT, they are not ordinarily affected by the NE released from sympathetic nerve endings, which affects largely the arterioles and arteriovenous anastomoses. It follows that increased reactivity to circulating AT in essential hypertension must occur because of some action not on the precapillary sphincters but on more proximal arteries, and again points to a defect in neural storage.[62, 71] There is, in fact, considerable evidence that AT does enter the peripheral NE neural store, and that a defect in this store is responsible for the increased reactivity both to NE and AT found in patients with essential hypertension.[62, 64, 7, 7] As evidence of this, one can cite the increased response to tyramine after prior infusion of AT in dogs,[7] and also the peculiar neurogenic type of hypertension that can be produced by chronic infusion of subhypertensive amounts of AT. Also AT I[131] studies show an increased store of AT as manifested by a slower than normal disappearance rate of labeled AT[62] despite a greater than normal in vitro degradation of either the labeled[61, 66] or unlabeled[61] AT by serum from hypertensive patients. These data, plus the increased disappearance rate of H[3] NE in essential hypertension,[62] again suggest a storage defect as the initiating mechanism in essential hypertension. It should be pointed out that increased reactivity has been demonstrated in the nonhypertensive children of parents with essential hypertension.[63]

How then are we to explain the hypertension that is associated with renal disease in man which is apparently characterized by

normal reactivity? If in fact, hypertrophy of smooth muscle is a factor that raises reactivity slightly one would have to consider intrinsic reactivity on a biochemical basis in renal hypertension to be even below normal levels. Hypervolemia and increased cardiac output account for most of the hypertension of acute glomerulonephritis,[84-87] and this is presumably due to the retention of salt and water because of the disease. In renovascular hypertension and in accelerated essential hypertension with nephrosclerosis, renin may be produced in excess[84-86] and may elaborate AT in excess. The AT may increase blood pressure by direct vasoconstriction.[84] It may also enter the NE storage pool and increase blood pressure after release from the nerves by nerve discharge.[77] It may also stimulate the production of aldosterone[77-] and increase blood volume and cardiac output and also reactivity slightly in some cases because of the retention of sodium. The latter however seems to be unlikely in view of the normal vascular reactivity observed in most cases. AT also acts on the renal tubules directly influencing the excretion of electrolytes in a complex manner.[illegible] The hypertension associated with polycystic kidneys has never been adequately studied in this respect but in chronic glomerulonephritis, pyelonephritis, lupus nephritis, and Kimmelstiel-Wilson's disease evidence that the hypertension is mediated through the renin-angiotensin system is unsatisfactory at present.[illegible] In these diseases there may be a general red vascular process of immunologic character in all small vessels including the renal ones,[illegible] or unknown factors may be involved. The suggestion[illegible] that autoregulation is involved as a response to an initial increase in cardiac output has not as yet been proved in man. Vascular reactivity is generally normal or only slightly increased in all of these conditions[illegible] provided that the case is pure and uncomplicated by essential hypertension and provided that testing is done after inhibition of sympathetic nerve discharge and by measurement of flow as well as pressure. Calculations, moreover must take into account some of the variables in this procedure such as changes in venous pressure and critical closing pressure and the level of the distending intravascular pressure itself apart from the pressure flow ratio. The latter by itself is merely at best an index of vascular caliber.[illegible] If identical changes in caliber take place against a higher intravascular pressure for example the force and work of vasoconstriction are obviously greater. If such considerations are kept in mind when studies are performed the results in renal hypertension will usually be within normal limits.

Summary

1 Vascular reactivity in man has been studied under many different conditions with a variety of methods.

2 The most productive methods [illegible] either intra arterial or intravenous infusion after inhibition of sympathetic nerve discharge and interpret changes in flow and pressure in terms of work of vasoconstriction rather than resistance

3 With the use of such methods vascular reactivity to various substances including l-norepinephrine (NE) and angiotensin II (AT) has been found to be increased in essential hypertension but not in various types of renal hypertension. Other methods have yielded equivocal and often contradictory results.

4 Reactivity in the digit measured by the work method can be decreased in essential hypertensive patients by salt depletion with a variable effect in normotensive subjects. Guanethidine and alpha methyldopa increase reactivity although they decrease blood pressure. Glucocorticosteroids increase reactivity in normotensive subjects but not in patients with essential hypertension, whereas aldosterone and salt increase reactivity particularly in the hypertensive group and only slightly in the normotensive group

5 Evidence is accumulating to implicate the renin-angiotensin system in renovascular and accelerated essential hypertension with nephrosclerosis. In hypertension secondary to various types of parenchymatous renal disease immune reactions in the blood vessels seem to be involved. Other theories are discussed

REFERENCES

1 Dahl, L. K. Heine M [illegible] and Tassinari, L Effect of chronic excess salt ingestion vascular reactivity in t[illegible] strains of rats [illegible] opposite genetic susceptibility t[illegible] experimental hypertension, Proc. Council for High Blood Pressure Re-

search, America Heart Association 12 11 1963
2. McGiff J C nd It L.vitz, H D Loss of renal soconstrictor activ ty of angiotensin II during ren l ischemia, J Clin Invest 43:2359 1964
3 Duff R S Some haracteristics of peripheral arterioles human h pertension, Harington, M editor H poten ive drugs, London nd New Y rk 1957 Pergamon Press p 196
4 Von E ler I S Noradrenaline Springfield, Ill 1956 Cha les C Thomas
5 Laragh J H Cannon, P J nd Ames, R P I teraction bet een aldosterone secretion, sodium nd pota ium balance, and angiotensin activit ma tudies in h pertension and cirrhosis Canad M A J 90:248, 1964
6 Cob J N Liptak, T E nd Frees E. D Hemod namic effect of guanethidine in man, Circulation Res 12:298, 1963
Grob D Scarborough W R Kalt H A J and Lanf rd H G Further observations on the effects of utonomic blocking agents in h pertension II Hemod namic ballistocardiog aphic and electr cardiographic effects of hexmethonium nd pentamethonium Circulation 8 352 1953
8 Fmlet, J R Granson, K S Bell, D M nd Org in E S Use of piperoxan and Regitine as outine tests in patients th hypertension, J A M A 146 1383, 1951
9 Mendlow tz, M nd Naftchi, N Work of digital vasoconstriction produced by infused norepinephrine in primary hypertension, J Appl Ph siol 13:247 1958
10 Burch C E nd DePasquale, N P Angiotens II digital blood flow nd the precapillary and postcapillary blood vessels of man, Ann I t. Med. 58:278 1963
11 Doyle A E Fraser J R. E., and Marshall, R J Reactivit of forearm vessels to vasoconstricti substances in hyperten and normotens bjects, Clin Sc. 18 441 1959
12. Dern, P L and Lea erton, J The effect of ngiotens II on the clearance of radioiodine f om the kin in h pertension, J Lab & Clin Med 6 :265 1966
13. Barany F L Reactivity of the skin essel to noradrenaline nd ngiotensin in arterial hyper tension, Scandina J Clin. & Lab Invest. 15 317 1963
14 Moulton, R Spencer A G., nd Willoughby D A. Noradrenaline sensitivity in hypertension measured with adioactive sod um techniques, Brit. Heart J 20:224 1958
15. Gombos E. A., H let, W H., Bopp, P Goldring, W Bald in, D S., and Chasis, H Reactivity of renal nd ystemic circulation t vasoconstrictor substances in normoten ive and hypertensi bjects, J Clin. Invest 41:203 196
16. Fowler N O and Holmes J C. I lmonary pressor action of l-norepinephrine and ngiotensin, Am. Heart J 70:66, 1965.
1 Schmidt, C. F The cerebral circulation in health nd disease Springfield, Ill 1950, Charles C Thomas
18 Goldenberg, M Pines K. L., Baldwin, E. de F Greene, D G., nd Roh, C F The hemodynamic response of man to norepinephrine and epinephrine and its relation t the problem of hypertension, Am. J Med. 5 79., 1948.
19 Tuckman, J Mendlowitz, M and Naftchi, N E Systemic vascular reactivity to l-norepinephrine I preparation.
20 Hines, E. A J and Brown, G E A standard test for measuring the ariability of blood pressure its ignificance as an index of the prehypertensi stat Ann. Int Med :209 1933
21 Judson, W E Epstein, F H and Wilkins R W The comparative effects of small intra enous doses of l-norepinephrine nd epinephrine upon arterial pressure nd pulse rate in normotensi subjects nd in hypertensive patients bef re and after thoracolumbar sympathectomy J Clin. I est 29 1414 1950
22. Pickering, G W and Kissin, M. The effects of adrenaline and of old on the blood pressure in human hypertension, Clin. Sc. 2:201 1936
23. Feisal, K. A. Eckstein J W Horsley A W and Keasling, H. H Effects of chlorothiazide on forearm vascular responses to norepinephrine J Appl. Physiol 16:549 1961
24. Mendlowitz, M Naftchi, N Wolf R. L., and Gitlow S E. Reactivit of the digital blood essel t angiotensin II in normotensive and hyperten ive subject Am. Heart J 6 :221 1961.
25 Folkow B Structural, myogenic, humoral, and nervous factors controlling peripheral re i nce n Harington, M editor Hypertensi drugs, London and New York, 1956, Pergamon Press p. 163
26. Redleaf, P D and Tobian, L. The question of hyperresponsiveness in hypertension, Circula tion Res 6 185 1958.
27 Mendlowitz, M Intra ascular re istance (Ed torial) Am. J Med. 26 463 1954
28. Genest, J Biron, P Boucher R. Kow E Nowaczynski, W and Chrétien, M Hyper tension and the endocrine tem Brest A. N and Moyer J H editor Hyperten ion, ecent ad ances Philadelphia, 1961 Lea & Febiger p. 6
29 Smith, J R and Hoobler S. W Acute and chronic cardiovascular effect of pent linium in hypertensi e patient Circulation 14 1061 1956.
30. Brod, J Fencl, V Hejl, Z., Jirka, J and Ulrych, M General nd regional haemod namic pattern underl ing essential hypertension Clin. Sc. 23:339 1962
31 Kaplan, S M Gottschalk I A., M gliorco, B R bovit, D and Ross, W D Hostilit in erbal productions nd hypnotic dreams of hypertensi patients (comparisons bet een h perten h nd normotensi gr ups nd ithin h pertensi individual) I ychosom. Med. 22 320, 1960
32. Shapiro, A P I y hophysiologic mecha ms in hypertensive v scular dise se Ann. I t. Med 53:64 1960
33. Yamada, S and Burton, A. C. Effect of re duced tissue pressure on bloo l flow of the

fingers the veni-vasomotor reflex, J Appl. Physiol. 6:501 1954.

34. Gaskell, P and Krisman, A. M.: Critical closing pressure of vessels supplying loops of the nailfold, Circulation Res. 6:461 1958.

35. Mendlowitz, M Torosdag S M and Sharney L. The force and work of digital arteriolar vasoconstriction in hypertension, J Appl. Physiol. 10:436, 1957

36. Ashton, H Critical closing pressure in hypertension, Clin. Sc. 22:89 1962.

37. Mendlowitz, M Naftchi, N E., Gitlow S. E., and Wolf R. L. Vascular responsiveness in hypertensive and hypotensive states, Geriatrics 20 797 1965

38. Mendlowitz, M., Naftchi, N E., Gitlow S. E Wolf, R L., and Tuckman, J Effect of tyramine on the digital circulation in normotensive and hypertensive subjects Dis. Chest 50:335 1966.

38a. Hickam, J B and Fraser R. Studies of the retinal circulation in man. Observations on vessel diameter arterial venous oxygen difference, and mean circulation time, Circulation 33:302, 1966.

39. Tuckman J Slater S and Kapfer S. Comparison of blood volume increase in the leg and change of cardiac output during tilt in normotensive and hypertensive man, Fed. Proc. 25:267 1966

40. Imbriglia, J E. Pathology of hypertension as generalized vascular disease, in Moyer J H., editor Hypertension, Philadelphia, 1959 W B. Saunders Co., p 3.

41. Mendlowitz, M Digital vascular resistance in normal, hypertensive and polycythemic states, Circulation 3:694 1951

42. Ostfeld, A. M Psychometric testing in hypertension, Proceedings of the International Symposium on the Epidemiology of Hypertension, New York, 1966, Grune & Stratton, Inc.

43. Greisman, S E. The relation of angiotensin and l-norepinephrine to essential hypertension as determined by the reaction of the nailfold capillary bed, J Exper Med 103:477 1956.

44. Lee, R E., and Holze, E. A. Peripheral vascular hemodynamics in the bulbar conjunctiva of subjects with hypertensive vascular disease, J Clin. Invest. 30:539 1951

45. Cole, D R and Gough, K. R. The critical closing pressure of blood vessels of the fingers in hypertensive and normal subjects, Clin. Sc. 19:587 1960

46. Ashton, H The minimum critical closing pressure of the digital blood vessels in hypertension, Clin Sc 28:385 1965

47. Jablons, B Manulet, P E Hahn, E. S Nakvasich, P and Salvo, R C. Angiotensin skin test in normotensive and hypertensive humans, Circulation 22 767 1960.

48. Mendlowitz, M and Naftchi, N E. Digital vascular reactivity to tyramine in normotensive and hypertensive subjects, Fed. Proc 25:625, 1966

49. Mendlowitz, M Naftchi, N Weinreb, H L., and Gitlow S. The effect of prednisone and prednisolone on reactivity of the digital vessels to l-norepinephrine in normotensive and hypertensive subjects, J Appl. Physiol. 16:89 1961

50. Mendlowitz, M. Naftchi, N E., Bobrow E. B. Wolf R. L., and Gitlow S. E. The effect of aldosterone on electrolytes and on digital vascular reactivity to l-norepinephrine in normotensive, hypertensive, and hypotensive subjects, Am. Heart J 65:93 1963.

51. Mendlowitz, M Naftchi, N E., Wolf, R. L., and Gitlow S. E. The effect of guanethidine and of alpha-methyldopa on the digital circulation in hypertension, Am. Heart J 69 731 1965

52. Freis, E. D Clinical pharmacology and use of chlorothiazide in the treatment of hypertension, in Moyer[40] p. 545.

53. Mendlowitz, M Naftchi, N Gitlow S E., and Wolf R. L. The effect of chlorothiazide and its congeners on the digital circulation in normotensive subjects and in patients with essential hypertension, Ann New York Acad. Sc. 88:964 1960.

54. Abboud, F M., Eckstein, J W and Pereda, S A. Acute hemodynamic responses to intravenous and intra-arterial guanethidine, Clin Res 9 136, 1961

55. Page, I. H The mosaic theory of hypertension, Reubi, F C Bock, K. D and Cottier P T editors Essential hypertension, Berlin, 1960 Springer Verlag, p 1.

56. Eisenberg S. The hypervolemic syndrome associated with acute glomerulonephritis, Clin Res. 6:292, 1958.

57. De Fazio, V Christiansen, R. C., Regan, T Baer L. J Monti, Y and Hellems, H. R. Circulatory changes in acute glomerulonephritis, Circulation 20 190 1959

58. Braun-Menendez, E Fasciolo, J C., Leloir L. F Munoz, J M., and Taquini, A. C Renal hypertension, translated by L. Dexter Springfield, Ill., 1946, Charles C Thomas

59. Mendlowitz, M Naftchi, N E., Wolf R L and Gitlow S. E. Vascular reactivity in the patient with essential hypertension and hypertension of renal origin, Am J Cardiol 9:680, 1962.

60. Kaplan, N M and Silah, J G. The angiotensin infusion test, a new approach to the differential diagnosis of renovascular hypertension, New England J Med. 271:536, 1964

61. Kaplan, N M and Silah, J G. The effect of angiotensin II on the blood pressure in humans with hypertensive disease, J Clin Invest 43:659 1964.

62. Wolf, R. L Mendlowitz, M Gitlow S. E and Naftchi, N E. Angiotensin II I[131] metabolism in normotensive and hypertensive human subjects, Circulation 23 754 1961

63. Wolf R L Mendlowitz, M Roboz, J Naftchi, N E and Gitlow S E. Recent studies on I[131]-labeled angiotensin II and analogues, Canad M A. J 90:295 1964

64. Gitlow S E Mendlowitz, M Kruk Wilk, E., Wilk, S Wolf R L., and Naftchi N E Plasma dl-β-H[3]-norepinephrine clearance in normal subjects and in patients with essential hypertension, J Clin. Invest. 43:2009 1964.

65. Mendlowitz, M., Gitlow, S. E., Wolf, R. L., and Naftchi, N. E.: On the integration of factors in essential hypertension, Am. Heart J. 67:397, 1964.
66. Fitz, A. F., Valenca, M., and Kirkendall, W. M.: Angiotensin infusion test (AIT) in normal and hypertensive subjects, Clin. Res. 13:206, 1965.
67. Moutsos, S. E., Perez Stable, E., and Shapiro, A. P.: Diagnosis and physiological implications of the angiotensin infusion test, Circulation 32:158, 1965.
68. Breckenridge, A.: Angiotensin-infusion test, Lancet 2:209, 1965.
69. Gorrno, W. E., and Kaplan, N. M.: Renal pressor material in various hypertensive diseases, Ann. Int. Med. 63:745, 1965.
70. McPhaul, J. J., Jr., McIntosh, D. A., Williams, L. F., Gritti, E. J., Malette, W. G., and Grollman, A.: Pressor activity of renal venous blood in hypertension, Ann. Int. Med. 61:847, 1964.
71. Brown, J. J., Davies, D. L., Lever, A. F., and Robertson, J. I. S.: Variations in plasma renin concentration in several physiological and pathological states, Canad. M. A. J. 90:201, 1964.
72. Veyrat, R., de Champlain, J., Boucher, R., and Genest, J.: Measurement of human arterial renin activity in some physiological and pathological states, Canad. M. A. J. 90:215, 1964.
73. Fasciolo, J. C., de Vito, E., Romero, J. C., and Cucchi, J. N.: The renin content of the blood of humans and dogs under several conditions, Canad. M. A. J. 90:206, 1964.
74. Gerolami, A., Mollura, J. L., and Cramer, Ch.: Evaluation of the angiotensin skin test, Am. Heart J. 70:377, 1965.
75. Carretero, A. C., Loyke, H., Hirakawa, A., and Kleinheuer, H.: Dermal responses to angiotensin. Similarity in normotensives and hypertensives, J. A. M. A. 184:711, 1963.
76. Hersting, C. G., Overdnson, P. J., Schirger, A., Sheps, S. G., and Fairbairn, J. F.: The angiotensin amide skin test: A nonspecific reaction, J. A. M. A. 186:153, 1963.
77. Mendlowitz, M., Gitlow, S. E., Wolf, R. L., and Tuckman, J.: The metabolism of hypertension, Am. Heart J. 70:677, 1965.
78. McCubbin, J. W., and Page, I. H.: Neurogenic component in chronic renal hypertension, Science 139:210, 1963.
79. McCubbin, J. W., De Moura, R. S., Page, I. H., and Olmstead, F.: Arterial hypertension elicited by subpressor amounts of angiotensin, Science 149:1394, 1965.
80. Wolf, R. L., Mendlowitz, M., Pick, J., Gitlow, S. E., and Naftchi, N.: In vitro degradation of I¹³¹-labeled angiotensin II by normotensive and hypertensive human serum, Proc. Soc. Exper. Biol. & Med. 109:308, 1962.
81. Hickler, R. B., Lauler, D. P., and Thorn, G. W.: Plasma angiotensinase activity in patients with hypertension and edema, J. Clin. Invest. 42:635, 1963.
82. Gitlow, S. E., Mendlowitz, M., Kruk Wilk, E., Wolf, R. L., and Wilk, S.: Metabolism of dl-β-H³-norepinephrine in patients with high blood pressure, Proc. Council for High Blood Pressure Research, American Heart Association, Hypertension 13:31, 1965.
83. Doyle, A. E., and Fraser, J. R. E.: Essential hypertension and inheritance of vascular reactivity, Lancet 2:509, 1961.
84. Judson, W. E.: Pressor activity of dialyzed plasma of patients with primary and secondary (renal) hypertension, Am. J. Cardiol. 9:710, 1962.
85. Gross, F., Schaechtelin, G., Brunner, H., and Peters, G.: The role of the renin-angiotensin system in blood pressure regulation and the kidney function, Canad. M. A. J. 90:258, 1964.
86. Morris, R. E., Jr., Robinson, P. R., and Scheele, G. A.: The relationship of angiotensin to renal hypertension, Canad. M. A. J. 90:272, 1964.
87. Davis, J. D., Carpenter, C. C. J., and Ayers, C. R.: Relation of renin and angiotensin II to the control of aldosterone secretion, Circulation Res. 11:171, 1962.
88. Biron, P., Koiw, E., Nowaczynski, W., Brouillet, J., and Genest, J.: Effects of intravenous infusion of valine 5-angiotensin II and other pressor agents on urinary electrolytes and corticosteroids, including aldosterone, J. Clin. Invest. 40:338, 1961.
89. Laragh, J. H., Angers, M., Kelly, W. G., and Lieberman, S.: Hypotensive agents and pressor substances, J.A.M.A. 174:234, 1960.
90. Peart, W. S.: Hypertension and the kidney. II. Experimental basis of renal hypertension, Brit. M. J. 2:1421, 1959.
91. Genest, J.: Angiotensin, aldosterone and human arterial hypertension, Canad. M. A. J. 84:403, 1961.
92. Fitz, A. E., Kirkendall, W. M., and Armstrong, M. L.: Plasma renin in renal parenchymal hypertension, Circulation 32:84, 1965.
93. Lange, K., Treser, G., Sagel, I., Ty, A., and Wasserman, F.: Routine immunohistology in renal disease, Ann. Int. Med. 64:25, 1966.
94. Taft, L. I., Dowen, J. K., and Mackay, I. R.: Localization and binding of serum proteins in glomeruli of kidney biopsies in disseminated lupus erythematosus and glomerulonephritis, Australasian Ann. Med. 7:5, 1958.
95. Koffler, D., and Paronetto, F.: Immunofluorescent localization of immunoglobulins, complement and fibrinogen in human disease. II. Acute, subacute and chronic glomerulonephritis, J. Clin. Invest. 44:1665, 1965.
96. Paronetto, F.: Immunocytochemical observations on the vascular necrosis and renal glomerular lesions of malignant nephrosclerosis, Am. J. Path. 46:901, 1965.
97. Freedman, P., Peters, J., and Kark, R. M.: Localization of gamma-globulin in the diseased kidney, Arch. Int. Med. 105:524, 1960.
98. Ledingham, J. M., and Cohen, R. D.: Changes in the extracellular fluid volume and cardiac output during the development of experimental renal hypertension, Canad. M. A. J. 90:292, 1964.

Fundamentals of clinical cardiology

A critical review of diagnostic tests for pheochromocytoma

Antoon Amery M.D
James Conway M.D
Ann Arbor Mich

The diagnosis of pheochromocytoma is suggested by the finding of paroxysmal hypertension accompanied by such symptoms as palpitation headache sweating and nervousness. In some patients however the syndrome presents with sustained hypertension making the diagnosis difficult. Since screening tests for pheochromocytoma are advisable in both paroxysmal and sustained hypertension it is thought that a critical review of the reliability of these tests would be of interest.

The pharmacologic tests with Regitine or histamine are of great value but both tests can be misleading and the reported incidence of false positive and false-negative tests is given in Table I

A third pharmacologic test, based upon the pressor response to tyramine was recently introduced but is not yet adequately evaluated

The high incidence of false negatives for the histamine test reported by Johns and Brunjes[4] occurs because in the interpretation of the tests the authors required the rise in pressure to exceed that achieved in the cold pressor test The frequency of false results particularly of false negative tests, has led to the search for more definitive tests by the analysis of the urine for catecholamines or their metabolites.

Urinary excretion of catecholamines Most of the methods used for the estimation of catecholamines in the urine are based upon the technique of von Euler[7] this includes absorption on aluminum elution with oxalic or acetic acid oxidation with potassium ferricyanide, and fluorometry The results obtained with these tests in patients with proved pheochromocytoma, and in persons without these tumors, are summarized in Table II From these figures it is apparent that values up to 643 micrograms per 24 hours can be found in persons without pheochromocytoma whereas patients with a proved pheochromocytoma can excrete as little as 64 micrograms per 24 hours.[8]

The frequency of *falsely negative determinations of catecholamines* in urine can be established by calculating the percentage results under the upper normal limit in patients who were found to have a pheochromocytoma at operation or at autopsy the reported percentages are zero up to 25 per cent.[11]

Several reasons for this scatter are apparent. Urine from a patient having pheochromocytoma with intermittent secretion and paroxysmal hypertension can be expected to have a normal concentration of catecholamines if collection is made during a period without attacks. Some pheochromocytoma tumors contain a catechol-o-methyltransferase and release primarily

Received for publication Feb 4, 1964.
Address Department of Medicine, University of Michigan Medical Center Ann Arbor Mich.

Table I. Pharmacologic test

Test	Incidence of	
	False positive	*False negative*
Histamine	2%(1)	8%(2), 12%(1), 75%(5)
Regitine	0%(3), 4%(4), 9%(1)	0%(4), 8%(5), 11%(2), 17%(1), 50%(3)

Table II. Urinary excretion of catecholamines (gamma per 24 hours)

Reference	Controls			Pheochromocytoma	
	Number of determination	*Mean and standard deviation*	*Range*	*Number of determinations*	*Range*
8	647	119 ± 73	10–643	9	64 2 750
9	114	32 ± 18	Up to 117	23	200–30 000
10	Not given		15–30*	Not given	180–9 000
	Not given		15–185†		

*Normal persons at rest

†Normal persons and hypertensive subjects at rest or working

the methylated form the urine then contains mostly (nor)metanephrine and only a slightly elevated (nor)epinephrine content.

The frequency of *falsely positive urinary excretion of catecholamines* is more difficult to establish since final proof at operation or autopsy is not always available. The reported frequency is low (2 per cent) when precautions are taken to eliminate situations which could increase the excretion of catecholamines.

The endogenous secretion of catecholamines is increased in stress emotions hypoglycemia[12] and exercise. Muscular exercise can increase sevenfold the output of catecholamines.[13] A transient hypotensive period even if provoked by vasodilators, such as Regitine causes an increase in the excretion of catecholamines. However it should be recognized that stress does not usually elevate the urinary excretion of catecholamines sufficiently to produce a false positive result for pheochromocytoma.

Exogenous sources of catecholamines which should be eliminated before urine is collected for the determination of catecholamines are bananas and certain drugs known to contain serotonin dihydroxyphenylalanine dopamine, and norepinephrine. The ingestion of even three bananas can increase the urinary excretion of total catecholamines to abnormal levels.[7,14] Certain drugs that contain catecholamines for example nose drops and bronchodilator drugs, can cause high urinary levels of catecholamines.

Other drugs interfere with the simplified catecholamine determinations which rely upon the fluorescent properties of catecholamines. These drugs are alpha methyldopa[14] tetracycline chlortetracycline erythromycin and oxytetracycline[7] chlorpromazine[15] and quinidine[7]. An excess of biliary pigment in the urine may interfere in the chromatographic determination of catecholamines.

The reasons for *false-positive plasma levels of* catecholamines are analogous to those for false-positive urinary levels furthermore elevated blood levels have been reported in patients with uremia[3,16] in patients with increased intracranial

pressure[11] and in patients with lymphoma,[21] lymphoblastoma and chemodectoma.[22] Nevertheless, determinations of catechol amines performed on samples of blood ob tained from different veins can be helpful for the localization of the tumor before the operation.[22]

Since the normal excretion of catecholamines can occur in the presence of a pheochromocytoma, and since high urinary and plasma levels of catecholamines may be misinterpreted attention has turned to the metabolic products of catecholamine metabolism such as VMA (= 3-methoxy 4-hydroxymandelic acid).

Excretion of vanilmandelic acid. Two basic methods for determining VMA in urine have been described. One[23] consists in a coloration with diazotized p-nitro aniline. In the other[8] the VMA is oxidized to vanillin and this substance is measured in an indole-induced color reaction.

The results of the determinations of VMA in the urine of patients with and without pheochromocytoma are summa rized in Table III. This table shows that up to 7.1 mg. of VMA can be excreted in the urine per 24 hours in persons without pheochromocytoma, whereas values as low as 4 mg. are found in patients with pheochromocytoma. Falsely negative VMA results are reported in varied frequency from zero[1,11,20] to 13 per cent. The follow ing factors decrease VMA readings and could contribute to falsely negative tests.

It has been found that in patients with a pheochromocytoma secreting primarily norepinephrine[9] relatively little VMA will be excreted in the urine. Since the me tabolism of the catecholamines may vary in different tumors, the possibility should always be borne in mind that a normal VMA value may occur with an abnormal excretion of catecholamines, and vice versa.

Certain drugs have been reported to decrease the urinary excretion of VMA. For example alpha methyldopa has been shown to decrease it in patients with essential hypertension.[26] In patients with pheochromocytoma however the reduc tion has been minimal[27] or only transient.[28] Monoamine-oxidase inhibitors such as iproniazid (Marsilid) decrease the urinary excretion of VMA, although a transient increase at the start of treatment may occur in some patients.[29] This drug will not reduce the excretion of VMA to normal levels in patients with a pheochromocy toma.

The frequency of falsely positive de terminations of VMA ranges from zero[22] to 5 or 6 per cent. The following con ditions increase VMA readings and thus lead to a falsely positive pheochromocy toma test. In serious illnesses, such as pulmonary insufficiency metabolic tumors, and shock, the production of VMA may be increased.[30] In metastatic carcinoid ganglioneuroma and neuroblastoma there

Table III. Urinary excretion of VMA

Reference	Control		Patients with pheochromocytoma	
	Number of determinations	*Results*	*Number of determinations*	*Results*
1	Not given	1.5–3 γ per mg. of creatinine	Not given	9–90 per mg. of creatinine
3	17	Up to 15 γ per mg. of creatinine	6	5–62 per mg. of creatinine
7	20	3.7 ± 1.1 mg. per 24 hr Up to 7.1 mg. per 24 hr	23	4–500 mg. per 24 hr
15	51	0.5–3.04 per mg. of creatinine	30	6–40 γ per mg. of creatinine or 4.4–5.7 mg. per 24 hr
16		0.5–4.0 γ per mg. of creatinine 2.3 mg. per 24 hr	41	5–40 per mg. of creatinine
20	21	1.4–4.7 mg. per 24 hr (95% range)	16	7–192 mg. per liter [illegible]
24	171	0.5–8.6 mg. per 24 hr	6	11–115 mg. per

may be an increase in the excretion of VMA.[20] Ingestion of various foods, citrus fruits, coffee, tea, chocolate, vanilla, bananas are reported to enhance the excretion of VMA. The interference of these food constituents applies especially to the screening techniques in which VMA is measured as vanillin[3] but not to the methods using the diazo reagent. The muscle relaxant methocarbamol[21] administered in a dose of 4 Gm. increases the VMA measured with the diazo reagent up to 15.4 mg. if the urine is collected after several days of treatment; it does not interfere when added in vitro to the urine. Para-amino-salicylic acid[22] administered in vivo or added in vitro will increase the VMA readings in the same test up to more than 100 mg. per 24 hours. The BSP and PSP reagents used as liver or kidney function tests can cause color to appear during certain steps in the determination. If this dye is not completely extracted, it can interfere in the colorimetric methods used for determinations of VMA. It is apparent that the excretion of VMA is valuable in the diagnosis of pheochromocytoma. Its accuracy is similar to the catecholamine test. It is a simpler method and this recommends it as a screening test.

Summary

The chemical tests for pheochromocytoma give both false-positive and false-negative results in less than 10 per cent of patients. The reported incidence of false results, particularly of false negatives, obtained with the chemical tests is not substantially lower than the results obtained with the pharmacologic tests. In general, therefore, the tests should be used to complement each other, and when a pheochromocytoma is suspected, both pharmacologic and biochemical tests are advisable. In case of difficulty, the urine should be collected for a period of 3 hours after an attack (spontaneous or provoked by drugs) and analyzed for VMA *and* catecholamines.

REFERENCES

1. Goldenberg, M., Serlin, I., Edwards, T., and Rapport, M. M.: Chemical screening methods for the diagnosis of pheochromocytoma, Am. J. Med. 16:310, 1954.
2. Gifford, R. W., Kvale, W. F., Maher, F. T., Roth, G. M., and Priestley, J. T.: Clinical features, diagnosis and treatment of pheochromocytoma. A review of 76 cases, Mayo Clin. Proc. 39:281, 1964.
3. Hutchinson, G. B., Evans, J. A., and Davidson, D. C.: Pitfalls in the diagnosis of pheochromocytoma, Ann. Int. Med. 48:300, 1958.
4. Gifford, R. W., Roth, G. M., and Kvale, W. F.: Evaluation of new adrenolytic drug (Regitine) test for pheochromocytoma, J.A.M.A. 149:1628, 1952.
5. Johns, V. J., and Brunjes, S.: Pheochromocytoma, Am. J. Cardiol. 9:120, 1962.
6. Engelman, K., and Sjoerdsma, A.: A new test for pheochromocytoma, J.A.M.A. 189:81, 1964.
7. Von Euler, U. S., and Floding, I.: Fluorimetric estimation of noradrenaline and adrenaline in urine, Acta physiol. scandinav. 33(Suppl. 118), 57, 1955.
8. Bollman, J. L., Flock, E. V., Roth, G. M., and Kvale, W. F.: Catecholamines in patient with pheochromocytoma, J. Lab. & Clin. Med. 56:506, 1960.
9. Crout, J. R., Pisano, J. J., and Sjoerdsma, A.: Urinary excretion of catecholamines and their metabolites in pheochromocytoma, AM. HEART J. 61:375, 1961.
10. Hingerty, D.: Thirty-minute screening test for phaeochromocytoma, Lancet 1:766, 1957.
11. Jacobs, S. I., Sobel, C. H., and Henry, R. J.: Excretion of 3-methoxy-4-hydroxymandelic acid and catecholamines in patient with pheochromocytoma, J. Clin. Endocrinol. 21:315, 1961.
12. Von Euler, U. S.: Quantitation of stress by catecholamine analysis, Clin. Pharmacol. & Therap. 5:398, 1964.
13. Von Euler, U. S., and Hellner, S.: Excretion of noradrenaline and adrenaline in muscular work, Acta physiol. scandinav. 26:183, 1952.
14. Crout, J. R., and Sjoerdsma, A.: Catecholamine excretion after banana feeding, J. Pharm. & Pharmacol. 11:190, 1959.
15. Crout, J. R., and Sjoerdsma, A.: The clinical and laboratory significance of serotonin and catecholamines in bananas, New England J. Med. 261:23, 1959.
16. Gifford, R. W., and Tweed, D. C.: Spurious elevation of urinary catecholamines during therapy with alpha-methyldopa, J.A.M.A. 182:493, 1962.
17. Neil, D. W., Carre, I. J., McCorry, R. L., and Thompson, R. H.: Possible source of error in diagnosis of pheochromocytoma, J. Clin. Path. 14:415, 1961.
18. Roth, G. M., Flock, E. V., Kvale, W. F., Waugh, J. M., and Ogg, J.: Pharmacologic and chemical tests as used in the diagnosis of pheochromocytoma, Circulation 21:769, 1960.
19. Sobel, C. H., and Henry, R. J.: Determination of catecholamines (adrenaline and noradrenaline) in urine and tissue, Am. J. Clin. Path. 27:240, 1957.
20. Emlet, J. R., Grimson, K. S., Bell, D. M., and

Orgain, E. S. Use of piperoxan and Regitine as routine tests in patients with hypertension J A M.A 116 1383 1951

21 Kvale W F Roth, G M M nger W M and Priestley J T Pheochromocytoma, Circulation 14:622 1956.

22 Vendsalv A. Studies on adrenaline nd nor adrenaline in plasma, Acta physiol. scandina 59:Suppl. 173, 1 1960.

23 Armstrong M D McMilla A and Shaw K. N F 3-Methoxy-4-hydroxy D-mandelic acid, urinary metabolite of norepinephrine Biochim. et biophy cta 25:422 1957

24. Sunderman, F W Clev land, P D Norman, C. L nd Sunderman, F W A method for the determination of 3-methoxy-4-hydroxy mandelic acid (VMA) for the diagnosis of pheochromocytoma, Am. J Clin. P th 34:293, 1960.

25 Gitlow S. E., Mendlowitz, M Khassis, S. Cohen, G and Sha, J The diagnosis of pheochromocytoma by determination of urinary 3-methoxy-4-hydroxymandelic acid, J Clin. Invest. 39:221 1960.

26. Tyce G. M Sheps, S G., and Flock, E. V Determination of urinary metabolites of catecholamines after the administration of methyl-dopa, Proc. Staff Meet. M y Clin 38:571 1963.

27 Gellman, N A. Landau, S. J M lrow P J Friedewald, T W and D lessio, D J Unresectable pheochromocytoma Respons t d-methyl-dihydroxy L-phenylalanine J Chron. Dis 16:217 1963.

28. Sheps, S. G. Kottke B A. Tyce G. M and Flock, E. V Effect of methyldopa on the metabolism of catecholamines and tryptopha I tw cases of metastatic pheochromocytoma Circulation 28:804 1963.

29 Von Stud ltz, W Effect of Marsilid on excretion of 3-methoxy-4-hydroxy mandelic acid in man, scandinav J Clin. & Lab. I vest. 11:224 1959

30. Gitlow S. E. Mendlowit M Kruk E. and Khassis, S. Diagnosi of pheochromocytoma by assay of catecholamine metabolites, Circulation Res. 9 746, 1961

31 Campbell D J Sherbanink, R and Rigby J False positive reaction due t methocarbamol in the screening test for vanilmandelic acid, Clin. Chem. 10:447 1964

32. Amery A Personal observation 1965

33 Duk W M Phillip, M W Donald, J M and Borchell, B. R A norepinephrine-secreting glomic tissue tumor (chemodectoma) J A M.A. 193 108, 1965

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F Lyon

Reappraisal of digitalis Part V Evaluation of criteria for determining effect of digitalis in man

Alan F Lyon M D
Arthur C DeGraff M D
New York N Y

The digitalis glycosides are known to exert multiple effects on the cardiovascular system These include hemodynamic effects on cardiac muscular contractility venous return and arteriolar resistance electrophysiologic effects, both direct and vagally mediated and effects on automaticity refractoriness and conductivity that differ not only in different parts of the heart, but with different doses of digitalis. Direct evidence of many of these effects is not available to the clinician and he has been forced in the past and is to a considerable extent still forced to evaluate the effects of digitalis in his cardiac patients by such crude parameters as improvement in congestive heart failure and decrease in the ventricular rate in the presence of atrial fibrillation. Through the use of these crude indices it has been noted that the amount of digitalis required initially to produce a measurable effect is much larger than that required to maintain that effect. In view of the slow and limited rate of excretion and metabolism of the digitalis glycosides used for chronic treatment, it has been assumed that an initial large dose is required to produce a tissue concentration adequate to cause the desired physiologic effect and that a much *smaller maintenance dose* is required to balance excretion and maintain tissue concentration and physiologic effect That this small maintenance dose does exert a physiologic effect is quite apparent in the patient with atrial fibrillation since the ventricular rate can be kept slow as long as these relatively small doses of digitalis are continued and when they are discontinued the ventricular rate accelerates at a rate comparable to the rate of dissipation of the glycoside involved On the other hand in the patient with sinus rhythm whose congestive heart failure has been relieved by digitalis, the value of continued low dosage of digitalis is much harder to establish clinically since initial relief of congestive heart failure may lead to physiologic changes that persist long after all digitalis has been excreted Although the general clinical impression is that low-dosage maintenance therapy is important and valuable objective hemodynamic assessment is usually not possible.

The estimation of both the initial digitalizing dose and the maintenance dose is of great practical significance since unlike most other commonly used drugs the margin between the dose that produces toxicity and that which produces clinically measurable beneficial effect is narrow usually of *the order of 3 2 Because of this*, an immense literature has developed that is con

Received for publication Oct. 10, 1964.
*Chief Cardiology Section, Veterans Administration Hospital, Bronx, N Y
**Professor of Therapeutics, New York University College of Medicine, and Consultant in Cardiology Veterans Administration Hospital, Bronx, N Y

cerned with the digitalizing and maintenance doses of various digitalis glycosides given by different routes and at different rates. Although these studies present schedules of average typical doses the requirements in individual patients vary widely and the clinician must learn by experience to individualize dosage It is this need for individualization that has led to confusion The criteria by which the physician must achieve this individualization are often quite tenuous.

Use of the ventricular rate in atrial fibrillation Most of the published clinical studies use subjects with atrial fibrillation since these patients provide in the slowing of the ventricular rate a convenient index of one of the electrophysiologic effects of digitalis. Yet there is no unanimity as to what ventricular rate should be the proper end point and there seem to be definite differences between patients as to the most suitable rate for control of symptoms. Some patients with mitral stenosis are most comfortable at very slow rates for instance below 50 per minute probably because the long periods of diastole that result allow for more adequate emptying of the left atrium Other patients who have atrial fibrillation without valvular disease are sometimes most comfortable at exceptionally slow rates probably because only the levels of digitalis that result in such slow rates produce an optimal increase in contractility The action of digitalis on the ventricular rate in atrial fibrillation can be considered to be a factor limiting digitalis rather than a general index of over all digitalis effect, and certainly the doses needed in this situation cannot be translated to the usual application of digitalis in patients in normal sinus rhythm and congestive heart failure

Use of improvement of congestive heart failure In patients with congestive heart failure digitalis dosage has been studied by estimating the amount of digitalis that produces an improvement in the congestive heart failure that is diuresis, when all other variables are kept constant. Such studies have usually been accomplished on hospitalized patients in whom diet and activity can be rigidly controlled. Valuable information on the average and range of therapeutic and toxic doses has been obtained in this fashion.

The practical application of this information by clinicians is somewhat limited since despite the average requirements that have been established the dose for each patient must be individualized and the clinical setting is rarely as well controlled as the experimental one. Most patients with heart failure who are given digitalis are simultaneously treated by means of salt restriction reduction of activity and often diuretics, all of which can ameliorate congestive heart failure without the need for digitalis Then when improvement occurs it is not necessarily due to digitalis and the physician cannot be certain that adequate tissue concentrations have been achieved It is even more difficult to be certain that an appropriate maintenance dose has been chosen since either the recurrence of failure at one extreme or the appearance of toxicity at the other may develop quite slowly and both are affected by concurrent changes in activity electrolytes and the underlying heart disease. Thus data on dosage are at best a rough guideline and in practice the trial-and-error method must be used Trial and-error methods may result in either underdigitalization or digitalis toxicity intentionally or inadvertently It is quite apparent that a better end point than "therapeutic effect" is a practical necessity The therapeutic effect defined as that point at which diuresis and improvement occur is not a direct measure of a fixed degree of digitalis effect. Rather it is an index of that amount of increase in contractility and perhaps decrease in venous return that is necessary in that particular patient to make a change in cardiac output and intracavitary pressures. This point is very likely to be reached at a higher level of digitalis in a patient with more severe heart disease than in a patient with a lesser cardiac defect

Use of signs of increased contractility Ideally one would like to achieve that level of digitalization that would produce the maximal increase in force of contraction without inducing arrhythmias or other manifestations of overdosage since this maximal restoration of contractility would provide the best protection against future stress.

Because of the practical difficulties of clinical assessment of therapeutic effect, and

the theoretical advantage of measuring the direct effect of digitalis considerable attention has been given to the clinical estimation of changes in contractility produced by digitalis in the cardiac patient. Direct measurement of the speed of contraction can only be obtained from a pressure tracing recorded in the ventricular cavity and direct measurement of the force of contraction only from a strain gauge arch stitched into the ventricle. Both of these are obviously impractical in the routine care of patients. It has been found that the duration of various easily measured indices of the duration of systole are shortened in proportion to the degree of change in contractility. The systolic ejection time (the time from the upstroke of the carotid pulse to the dicrotic notch) and to some extent the interval between the first sound and second sound and the interval between the first sound and the carotid upstroke all reflect change in contractility. Unfortunately these secondary indices of contractility are a reliable measure of digitalis effect only in normal subjects. In the presence of congestive heart failure changes in flow and resistance also affect them in various ways and make clinical interpretation of them difficult.

Other techniques. Since assessment of contractility, which is the most direct index of digitalis effect, is not practical, other objective measures must be considered. Actual identification and quantification of digitalis in the blood can be accomplished only with the use of isotope-labeled glycosides; this is obviously not useful for clinical assessment. Changes in the electrocardiogram have no precise relation to the level of digitalization and cannot be used to adjust digitalis dosage.

Another physiologic approach to the titration of digitalis has been offered in which the effect of digitalis on slowing the entry of potassium into the cell is used to measure digitalis effect. In this technique the rate of disappearance of the stable isotope rubidium 86 (which is handled like potassium) from serum into red cells is measured and the deviation from normal is interpreted as digitalis effect, compared with tables, and reported as digitalis level. Unfortunately there has been no confirmation of the initial report and our efforts to duplicate the results, at least with digoxin, have been unsuccessful.

It can thus be concluded that the physician at the bedside has no precise way of assessing the effect of digitalis or the level in the tissues. Most of the problems in clinical usage of digitalis that will be discussed subsequently in this series can be related to this problem.

REFERENCES

1. Kay, C. F.: The clinical use of digitalis preparations, Circulation 12:116, 1955.
2. Weissler, A. M., Snyder, J. R., Schoenfeld, C. D., and Cohen, S.: Assay of digitalis glycosides in man, Am. J. Cardiol. 17:768, 1966.
3. Lowenstein, J. M.: A method for measuring plasma levels of digitalis glycosides, Circulation 31:228, 1965.

Preserving a medical document

The -ray film may be regarded as medical document containing anatomic data relevant to the time t which it was obtained It is frequently of diagnostic importance for the physician t his objective information in regard t the medical background of patient. The -ray film provides such information For example it may inform the cardiologist whether his patient heart was enlarged 5 or 10 year previously or whether an abdominal aortic aneurysm is of recent origin. Y t it the practice of most hospitals t discard -ray film after 3 to 5 years This has been necessary because of the vast number of -ray film taken each year T store -ray films for an indefinit period of time is beyond the capacity of most institutions. However it seems to us that, if physicians could arrange for hospitals t give patients their -ray films these documents could be preserved for the lifetime of the patient with no difficulty The patient could be instructed to place the -ray films on shelf in the linen closet where they could be forgotten until the physician requested them Furthermore if the patient moves, the physician in the new community would be spared the trouble of writing for the old -ray films and hospital personnel would be spared the incon enience of searching for and mailing them. However more important, the patient new doctor is guaranteed that the ld -ray film are ailable to him. Although written reports of -ra finding re of some benefit, they are no substitute for th -ray film itself when a recent -ra film is to be compared with one taken years previously

By the simple expedient of giving patients their -ray films for saf keeping this most ital of medical documents may be preserved and ailable to any physician for the lif time of the patient.

George E. Burch M D
Nicholas P. DePasquale M D
Department of Medicine
Tulane University School of Med ne
1430 Tulane Ave
New Orlea La 70112

Adrenergic receptors in the coronary circulation

Despit the fact that almost nothing is know about their physical structure the concept of pecific cellular sites (receptors) which interact ith hemical substances to produce definit pharmacologic effects has proved t be most usef l one. An t tractn hypothesis proposed by Ahlqui t, expla ns the cardiovascular actions of adren line and nor adrenaline in terms of tw different types of adrenotropic receptors situated on the blood essel Il Combination of these substances with α-receptors mediates asoconstriction, and with β-receptor asodil ta ion I general, combi tion w th α- nd β-adrenergic receptors mediates excita ory nd inhibitory responses respectively mporta exception however is the timulan ac ion adrenaline and noradrenaline on the myocard m which is mediated through interaction h β receptors.

U til quite recently little was know bout the existence of adrenergic receptors in the coronary ascular bed lthough clarification of this problem is importa t in iew of the widespread linical use of β-adrenergic blocking drugs It is pec liarl difficult problem to elucidate because although most workers in this field are agreed th the net effect of adrenaline and noradrenaline is to produce an increase in coronary blood flow the precise action on the vessels themselves has bee the subject of considerable controvers This ems from the fact that besides direct ac ion on the smooth muscle of the blood essel wall he mpathomimetic amines alter systemic art rial blood pressure heart rate and myocardial ontractile force (and, hence extravascular support nd cardiac ox gen consumption), and each of these factors can profoundl modify coronary flow These factors ould mask the direct action of adrenaline and no adrenaline on the essels themsel es.

A considerable amount of evidence has accumulated recently for the existence of both types of adrenergic receptors in the coronary vascular bed.[20,44] By measuring phasic flow in the cannulated left coronary artery of dogs perfused under constant pressure and estimating vasomotor activity within the coronary bed by recording end-diastolic flow, Douthell and his colleagues found that both isoprenaline and noradrenaline caused vasodilatation when infused into the coronary artery, and that these effects were profoundly altered by β-adrenergic blockade with pronethalol. A point of particular interest was that the vasodilator effect of noradrenaline was in fact reversed after β-adrenergic blockade to a vasoconstrictor action; this was interpreted as being due to stimulation of α-adrenergic receptors. Similar conclusions were reached by Parratt,[20] who measured myocardial (as opposed to coronary) blood flow in dogs and monkeys using a thermoelectric method. Intravenous infusions of adrenaline in doses which had no effect on blood pressure or heart rate usually lowered myocardial vascular resistance; after β-receptor blockade adrenaline led to increased myocardial vascular resistance. Noradrenaline was usually slightly vasoconstrictor before β-blockade and very markedly constrictor after it. These results were again interpreted as indicating the presence of both α- and β-adrenergic receptors in the myocardial vascular bed.

Another different interpretation of the reversal of adrenaline and noradrenaline vasodilatation by β-blockade has been proposed by Hashimoto and his colleagues.[17] Their suggestion was that sympathetic amines induce coronary vasodilatation through stimulation of myocardial metabolism, and that reversal by dichloroisoprenaline is due solely to blockade of these metabolic effects. In view of more recent evidence, however,[44,48] their conclusion that the presence of pure sympathetic vasodilator receptors in the coronary vascular bed is improbable cannot be upheld. Thus Hirche[44] has found that the infusion of very small amounts of adrenaline to the left coronary artery increased coronary sinus outflow and pO_2 without influencing heart rate, systemic pressure or cardiac contractile force, and similar effects have been observed in the isolated potassium-arrested heart, in which decreases in coronary vascular resistance due to metabolic effect were eliminated.[18] The conclusion that both types of adrenergic receptors exist and function in the coronary vasculature has also been reached by Gregg and his colleagues[18] Intracoronary injections of catecholamines in unanesthetized dogs caused large increases in coronary flow before any change in myocardial function and contractility occurred. In some very interesting experiments with isolated smooth muscle strips from coronary arteries of different sizes, Zuberbuhler and Bohr[48] have come to the conclusion that both types of receptors are present in the larger arteries, but that β-receptors predominate in the smooth muscle of the vessels of smaller diameter. This variation in the distribution of the two types of receptors in different parts of the vascular tree, the probability that the level of the coronary vascular tree which makes the major contribution to resistance to flow may vary with the species and with the physiologic state of the animal, and the possibility that different experimental approaches may favor either α- or β-receptor stimulation, could explain the many conflicting reports concerning the action of adrenaline on the coronary vessels.[48] Other factors which may also be involved are the different dose-dependent actions of catecholamines on resistance and capacitance vessels and on the muscle sphincters,[48] and the fact that with infusions of catecholamines different receptors are affected at different times, depending on the rate at which the substances combine with and leave the receptor and on their rate of destruction.

A very closely related problem with important clinical implications is whether adrenergic vasodilator fibers exist to the coronary vascular bed. If we are correct in the conclusion that β-adrenergic receptors predominate in the smaller coronary arteries, we would expect that the release of adrenergic transmitters from the rich sympathetic innervation to these vessels would result in a decrease in vascular resistance and an increase in coronary flow. Sympathetic vasodilator fibers to the coronary vessels in the cat and dog have been described by Szentivanyi and Juhász-Nagy.[48] the preganglionic fibers are believed to synapse in ganglia within the heart muscle. Since acetylcholine can be detected in the blood leaving the heart after stimulation of these fibers, and since the resulting vasodilatation is said to be blocked by atropine,[48] it has been suggested that these sympathetic postganglionic vasodilator fibers may be cholinergic—a situation rather analogous to that in skeletal muscle.[48] There is evidence, however, that acetylcholine can release adrenaline from cardiac tissue by a nicotine-like action on postganglionic adrenergic terminals, and the finding that the β-adrenergic blocking drugs pronethalol and propranolol markedly increase myocardial vascular resistance[20,48] suggests that the end transmitter released is in fact adrenaline. It is conceivable that the actual vasodilator fibers are cholinergic and that we have here another example of the "double transmission" concept proposed by Burn and Rand.

It has been suggested that these vasodilator fibers are activated when there is a fall in perfusion pressure in the coronary vascular bed.[14] The normal relationship between perfusion pressure and flow in the coronary vascular bed is such that very little change in flow occurs when the perfusion pressure is reduced from about 120 to 40 mm. Hg.[20] This "autoregulation" is abolished or modified by the injection of procaine around the stellate ganglia, by β-receptor blockade of the myocardial vascular bed,[20] by depleting the cardiac tissue of catecholamines, and by preventing their release from cardiac sympathetic nerves with adrenergic neurone blocking agents.[18] These findings suggest that the autoregulation in the coronary vascular bed is mediated through adrenergic vasodilator fibers. These fibers are also probably activated during excitement[48] and after stimulation of the brain stem.[48]

Substances that block β-adrenergic receptors decrease myocardial blood flow in the dog and

monkey.[25,26] This could be the result of a reduction either in sympathetic vasodilator tone or in the oxidative requirements of the myocardium resulting from the reduction in contractile force.[17,26] As has been previously pointed out,[26] it is impossible to state categorically which of these two factors is primarily responsible but the existence of β-receptors in the coronary vascular bed, the very marked decrease in flow observed and the fact that coronary sinus pO_2 decreases after β-blockade[27] all suggest a predominant effect on the vessels themselves.

Propranolol and pronethalol have been used in the treatment of angina pectoris but the initial claims of effectiveness[2,12,16] have not been confirmed in other studies.[4,20,27,41] A particular problem associated with the use of these drugs is apparent from the conclusion that α- as well as β-adrenergic receptors are present in the coronary vascular bed. Patients with angina may be quite happy with propranolol, but any procedure that would lead to the release of adrenaline and noradrenaline from cardiac nerves or from the adrenal medulla could result in coronary vasoconstriction by an effect on the coronary α-adrenergic receptors.[25,26] It is just conceivable that this may be a factor in the few cases of cardiac failure which have been reported after the administration of β-adrenergic blocking drugs,[20,29,40] particularly since there is some rather disturbing evidence that these substances can also reduce the vasodilator effects of myocardial hypoxia.[14]

J. R. Parratt, B.Pharm., M.Sc., Ph.D.
Department of Physiology
University of Ibadan
Ibadan, Nigeria

REFERENCES

1. Ahlquist, R. P.: A study of adrenotropic receptors, Am. J. Physiol. 153:586, 1948.
2. Alleyne, G. A. O., Dickinson, C. J., Dornhorst, A. C., Fulton, R. M., Green, K. G., Hill, I. D., Hurst, P., Laurence, D. R., Pilkington, T., Prichard, B. N. C., Robinson, B., and Rosenheim, M. L.: Effect of pronethalol in angina pectoris, Brit. M. J. 2:1226, 1963.
3. Berne, R. M.: Regulation of coronary blood flow, Physiol. Rev. 44:1, 1964.
4. Besterman, E. M. M., and Friedlander, D. H.: Clinical experiences with propranolol, Postgrad. M. J. 41:526, 1965.
5. Burn, J. H., and Rand, M. J.: Sympathetic postganglionic cholinergic fibres, Brit. J. Pharmacol. 15:56, 1960.
6. Denthell, U.: Wirkung von Brenzcatechinaminen auf die Coronardurchblutung an narkotisierten Hunden. Pflügers Arch. ges. Physiol. 287:111, 1966.
7. Denthell, U., ten Bruggencate, H. G., and Kramer, K.: Coronarvasomotorik unter Noradrenalin und Isopropylnoradrenalin nach Blockierung der adrenergischen β-Receptoren durch Nethalide, Pflügers Arch. ges. Physiol. 281:181, 1964.
8. Folkow, B.: Effects of catechol amines on consecutive vascular sections, in Adrenergic mechanisms (Ciba Foundation), Boston, 1961, Little, Brown & Co., and London, J. & A. Churchill Ltd., pp. 190-198.
9. Folkow, B., Frost, J., Haeger, K., and Uvnäs, B.: Cholinergic fibres in the sympathetic outflow to the heart in the dog and cat, Acta Physiol. Scandinav. 15:421, 1948.
10. Folle, L. E., and Aviado, D. M.: Cardiovascular effects of cocaine and the influence of a new beta adrenergic receptor blocking drug, J. Pharmacol. & Exper. Therap. 119:79, 1965.
11. Gaal, P. G., Kattus, A. A., Kolin, A., and Ross, G.: Effect of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade, Brit. J. Pharmacol. 26:713, 1966.
12. Gillam, P. M. S., and Prichard, B. N. C.: Use of propranolol in angina pectoris, Brit. M. J. 2:337, 1965.
13. Ginsburg, J., and Cobbold, A. F.: Effects of adrenaline, noradrenaline and isopropylnoradrenaline in man. Adrenergic mechanisms, pp. 173-189.
14. Grayson, J., and Parratt, J. R.: A species comparison of the effects of changing perfusion pressure on blood flow and metabolic heat production in the myocardium, J. Physiol. In press.
15. Pitt, B., Elliot, E. C., and Gregg, D. E.: Hemodynamic effects of catecholamines on the coronary circulation in the unanesthetized dog, Fed. Proc. 25:401, 1966.
16. Hamer, J., Grandjean, T., Melendez, L., and Sowton, G. E.: Effect of propranolol (Inderal) in angina pectoris: Preliminary report, Brit. M. J. 2:720, 1964.
17. Hashimoto, K., Shigei, T., Imai, S., Saito, Y., Yago, N., Uei, I., and Clark, R. E.: Oxygen consumption and coronary vascular tone in the isolated fibrillating dog heart, Am. J. Physiol. 198:965, 1960.
18. Hirche, H.: Die Wirkung von Isoproterenol, Adrenalin, Noradrenalin und Adenosin auf die Durchblutung und den O_2-Verbrauch des Herzmuskels vor und nach der Blockierung der β-Receptoren, Pflügers Arch. ges. Physiol. 288:185, 1966.
19. Hoffmann, F., Hoffmann, E. J., Middleton, S., and Talesnik, J.: Stimulating effect of acetylcholine on mammalian heart and liberation of epinephrine-like substance by isolated heart, Am. J. Physiol. 144:189, 1945.
20. Joss, F., Balmer, P., and Gobler, R.: Klinische Erfahrungen mit einem neuen herzwirksamen Sympatholyticum Nethalide, Cardiologia 44:144, 1964.
21. Juhász-Nagy, A., and Szentiványi, M.: Separation of cardioaccelerator and coronary vasomotor fibres in the dog, Am. J. Physiol. 200:125, 1961.
22. Kaiser, G. A., Ross, J., and Braunwald, E.: Alpha and beta adrenergic receptor mechanisms in the systemic venous bed, J. Pharmacol. & Exper. Therap. 144:156, 1964.
23. Kako, K., Krayenbühl, H. P., Lüthy, E., and Heggllin, R.: Cardiovascular effect of catechol-

amines in dogs before and after beta-adrenergic blockade. N un Schmiedeberg Arch. Exp P th 254:297 1964

24 Ka erina, N V Pharmacology of the coronary circulation, Oxford, 1965 Pergam n Press

25 Keela P Double-blind trial of propr nolol (Inderal) in ngina pectoris, Brit M J 1:897 1965

26. Klo k F J Kaiser G A Ross, J and Braunwald E A intrinsic adrenergic vasodilat r mechanism in the oronary scular bed of the dog Circulat n Res 16 376 1965

27 MacAlp R N Katt s, A A nd W field M F The effect of β-adre nerg -blocking gent (Nethalide) nd nitrogl cerin on exercise toler or in ngina pect ris Circ l tion 31:869 1965

28 Mendel D M ocardial scular reactivity Lancet 1:597 1966

29 Mora N C nd Perkins M E Adrenergic blockade of the mammalia he rt by dichlor analogue of soproterenol, J Pharmacol & E per Ther p 124 223 1958

30 Mosher L R J M I te, I A and Shaw R F C nt rol of oronary blood flow by a t areg lators mecha ism Circ la ion Res 14 250 1964

31 Parratt J R Blockade of mpathetic β-receptor in the m ocardial circul t on Brit J Pharmac l 24:601 1965

32. Parr t J R Studies on the mechanism of toreg lation of my ocardial bl od flow I prepar tion

33 Parr tt J R nd Grayson J My ocardial sc lar react ty after beta-adrenergic block ade Lancet 1:338 1966

34 Parratt J R nd Grayson J : Myocardial ascula reactivity Lancet 1:819 1966.

35 Prichard B N C. nd Gillam P M S. The use of propranolol in the treatment of hyper tension Brit M J 2 725 1964

36. Ra ford C R Khouri E M nd Gregg, D E Effect of excitement on coronary and stemic energetics in naesthetized d gs Am J Physiol. 209:680, 1965

37 Redding V J and Rees J R M ocardial asc lar reactivit Lancet 1:518 1966

38 Snow P J D Effect of propr nolol in myocardial infarct on Lancet 2:551 1965

39 Stock J P I nd D le N Beta-adrenergic recept r bl kage in ardiac arrhythmias, Brit M J 2 1230 1963

40. Stra t C B and Bruc R A. Nonspecific nd beta adrenergic blocking effect of Alderlin in ngina pecto s, Am Heart J 70 150 1965.

41 Szentiványi M and Juhász-Nagy A A new pect of the nervous cont l of the coronary bl d essels, Quart J Exper Phy iol 44:67 1959

42 Ueda, H Shimomura, K Goto, H Y soda, H Ito, K. Kat yama, S Ku one A nd Sugimoto, T Changes i oronary blood flow by tim lation f entral nervous tem, J p. Heart J 5 323, 1964

43 Uvnä B S mp thetic vasodilat r ystem and bl od flow Phy iol Rev 40:69 1960

44 Zuberbuhler R C nd Bohr D F Responses f oronary sm oth muscle t techolamines Circ lation Res 16:431 1965

Beta adrenergic blockade in patients with hypertrophic obstructive cardiomyopathy

The specific beta-adrenerg recept r tagonist propranolol selecti ly inhibits both the inotropic and hronotropic effect of adrenal ne on the heart Since there i now abundant evidenc that the heart in h pertrophic obstructi e cardiomy p thy i chronically nder the i fluenc of pathologically increased ympathetic dri the use f propr nolol f r long-term therapy of patient with hyper trophic obstructiv ardiomy p thy ha firm rat onal bas s. The hemody mic abnormal ty in hypertrophi obstructi ard my pathy tremely labile and readily mod fied both by physi ologic maneu ers and by drugs Although acut beta-adrenergic blockade usually ha little effect on the hemodynamic of the t nqu l p tient on the theterization table it has bee show to oppose the exac rbation in gradient induced by exercise or by infused adren line or isopren line It w thought therefore that the long term se of propr nolol might protect patien with hypert ophic obstructi cardiomyopathy from the isk of sudde de th by opposing surges of ympathetic timulation fter emotional tress or sudden exert on Since opposed ag l f fluence on the h art i hyper trophic obs ructiv ardiomyopathy ould be b most undesir ble hemic l utonomic dener t n of the hea t w ttempted by the combined use of propranolol nd propantheline

Thirteen of the 65 patients with hypertrophic obstructive cardiomyopathy who have been studied at Hammersmith Hospital were selected for this long-term medical treatment. They ranged in age between 6 and 45 years and had been treated with propranolol in doses of between 5 and 20 mg three times daily together with propantheline 15 mg three times daily as corrective. All of the patients were available for regular assessment of subjective response and auscultatory findings with phonocardiograms and arterial pulse records. The response to the Valsalva maneuver and to repeatable exercise test was noted.

No patient said that he was worse on the treatment and there were no prominent side effects. Eleven of 13 patients stated that they were better. Seven of 9 patients with effort dyspnea were improved. 5 of 6 patients lost their dizziness or syncopal attacks, and angina was relieved in the 2 patients who had it.

Physical examination revealed little change in resting patients although the intensity of the ejection type of systolic murmur diminished during treatment in 9 of the 13 patients. Examination during provocation with exercise or the Valsalva maneuver showed more convincing change since the murmur no longer became intensified. The second sound became normal in 3 of the 4 patients in whom it had been paradoxically split before treatment.

As has been noted before by Chamberlain there was a tendency for the heart to become larger during treatment with propranolol and this was observed radiologically in 10 of the 13 patients.

This preliminary study suggests that beta-adrenergic blockade may be of value in the long-term management of patients with hypertrophic obstructive cardiomyopathy although the unpredictable course of the disease makes it necessary for the study to be continued for much longer and in a larger series of patients before any firm conclusions can be drawn. The need to establish a firm diagnosis before starting treatment is of course mandatory for beta-adrenergic blockade can be harmful or even dangerous in diseases in which there is a risk of heart failure.

G. Cherian, M.D.
I. M. Brockington, M.R.C.P.
P. M. Shah, M.D.
C. M. Oakley, M.D., M.R.C.P.[**]
J. F. Goodwin, M.D., F.R.C.P.
Postgraduate Medical School
London W. 12 England

REFERENCES

1. Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. G.: Hypertrophic subaortic stenosis, Am. Heart Assoc. Monograph No. 10, New York, 1964, American Heart Association.
2. Pearce, A. G. E.: *In* Ciba Foundation Symposium on the Cardiomyopathies, p. 89, New York, 1964, Grune & Stratton, Inc.
3. Chamberlain, D. A.: *In* Imperial Chemical Industries Symposium on Propranolol, 1965.
4. Cherian, G., Brockington, I. M., Shah, P. M., Oakley, C. M., and Goodwin, J. F.: Beta-adrenergic blockade in hypertrophic obstructive cardiomyopathy, Brit. M. J. 1:895, 1966.

*Supported by a grant from the International Cardiology Foundation.
**Supported by the British Heart Foundation.

Mind stretching

I think I may define diseases are characterized traditionally by symptoms and signs which are manifestations of illness in the sense of the patient not feeling well. This ... has been fostered over ... preoccupation with acute illness and ... treatment. It has been supported further by the very nature of the relationship of the patient who ... the physician whose major task is to make him feel better. The pattern, however, is changing and is changing particularly with respect to the diagnosis and treatment of chronic disease. I propose to discuss some of these changing points of view especially as they affect arterial disease.

It is characteristic of arterial disease to be asymptomatic in its early stages. It is not until the disease progresses to the point of obstruction with ischemia of the tissues supplied with blood, or of rupture of weakened arterial walls, with hemorrhage and destruction of surrounding tissues, that symptoms appear. These symptoms may have their seat not in the artery itself but rather in the supplied or surrounding tissues. In addition, the major "enemies" of the arteries, those diseases, how artiller

constantly bombards them, are often also asymptomatic in their earliest stages. These diseases include essential hypertension diabetes mellitus, and gout among others. They characteristically become symptomatic the fourth and fifth decades of life but re recognized earlier because biochemical test or biophysical apparatus for their detection happens t be a lable t the present stage of medical development. It is known, moreover that these asymptomatic bnormal ties eventuate fre quently n such symptomatic diseases as renal fa lure, blindness, coma, nephrosis with edema, nd acute arthritis apart from their effect on arterial disease tself with the consequent catastrophes of stroke, heart ttack, or peripheral gangrene

Since all these diseases are t least part genetically determined it is clear that the bnormalities must be present from birth and the terms *prediabetes*, *prehypertension*, and *pregout* are beginning t ppear Methods for detecting such bnormalities re i arious stages of development. Hyperuricemia is easily determined nd there are new testing procedures for prediabetes such as the cortisone glucose tolerance test[1] prehypertension, ascular reactivity tests[2] and tritiated norepinephrine disappearance rates[4] are on the horizon. Thus, there ar whole group of bnormalities which are not symptom-producing but which may nd probably will eventually esult in symptomatic disease

There are many *predisease* states ther tha those lready mentioned. For example arterial disease is interrelated with spectrum of lipid bnormalities, w th certain personality haracteristics, w th abnormal steroid responses abnormal blood lotting nd w th such acquired habit as smoking mong other factors.

What is the real relationship of the *prediseases* t arterial disease itself? It is obvious that ery little is know bout this, since most of these conditions ha e only recently come t light It is possible for example that some young patients who dev lop oronary occlusion out of the blue so to speak, re i reality prehypertensive and that their h pertension has not yet become manifest bec use of carotid sinus and other baroreceptor inh bition of sympathetic outflow t mention only one of many possible relationships. Many thors have peculated on mechanisms in cases of arterial disease which precede overt manifestations of diabetes[10] etc.

This process of biochemical nd biophysical investigation of the etiology of hronic diseases is like peeling an artichoke ever-deepening layers. Since it is clear that the diseases discussed are often genetically determined the heart of the matter will not be clarified u til the chemical structure of the genes and their exact relationships to intracellular proteins are discovered.

Effective therapy meanwhile is largely in the realm of preventiv medicine There is no rational therapy for the *predisease* states in this sense except perhaps for hyperuricuria. When asymptomatic hypertension or diabetes is *discovered*, it is treated in order t regulate or to normalize abnormal blood pressure or blood sugar rather than to "cure. I this way it is believed that, at least to some extent, the arteries will be spared and the pace of their destruction diminished.

What is more, therapy itself may produce side actions which are more unpleasant than th disease itself nd patients must be conv nced t be treated on the basis of reason and knowledge rather than for relief of symptoms, huge educational process. Therapy may even produce diseases, such as hemolytic nemia, lupus erythematosus-like syndrome[11] or other imm nologic states,[12] the effects of which may t times be worse than the effects of the underlying disease left ntreated

All of this requires reorientation of teaching as well as of medical thinking i general. The mind must be stretched to adjust to the new medicine as it is and as it will undoubtedly develop.

Milton Mendlowitz, M D
Cl ical Professor of Medicine
The Mount S na School of Medicine
100th St. and Fifth Ave
New York N Y 10029

REFFRENCES

1 Fajans, S. S and Conn, J W An approach t the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone Diabetes 3:296, 1954.
2. Mendlowitz, M and N ftchi, N Work of digital vasoconstriction produced by nfused norepinephrine in primary hypertension, J Appl. Physiol. 13 247 1958.
3. Doyle, A. F nd Fraser J R E. Essential hypertension and inheritance of vascular reactivity Lancet 2:509 1961
4 Gitlow S. E. Mendlowitz, M Kruk Wilk E., W lk, S., Wolf R L., nd Naftchi, N. E. Plasma clearance of dl-β-H³-norepinephrine in normal human subjects nd patients with essential hypertension, J Cli In est. 43:2009 1964
5 Fredrickson, D S. Essential f milial hyper lipidemia, Sta bury J B Wyngaarden J B and Fredrickson D S editors The metabolic basis of inherited disease, New York 1960, McGraw Hill Book Co. Inc p. 489
6. Rosenman, R. H Friedman, M Straus, R Wurm M Jenkins, D Messinger H B Kositchek R Hahn, W and Werthessen, N T Coronary heart disease in the western collaborative group study J.A.M.A. 195:86, 1966.
7 Friedman M Byers, S. O nd Rosenman, R. H. Effect of corticotropin upon triglyceride levels Result in coronary prone subjects and patients with Addison disease J.A.M.A. 190:959 1964.
8. O Brien, J R. Platelet stickiness, Ann. Rev Med. 17 275 1966.
9 Doyle J T : Etiology of coronary disease Risk factors influencing coronary disease Mod. Concept Cardiovas. Dis. 35:81 1966
10. Rifkin H. Clinical impact of ins lin, Diabetes 12:31 1963.

11. Levine, B. B.: Immunochemical mechanism of drug allergy. Ann. Rev. Med. 17:23, 1966.
12. Lee, S. L., Rivero, I., and Siegel, M.: Activation of systemic lupus erythematosus by drugs, Arch. Int. Med. 117:620, 1966.
13. Ackroyd, J. F.: The immunological basis of purpura due to drug sensitivity. Proc. Roy. Soc. Med. 55:30, 1962.

Book reviews

COMA SINCOPE SHOCK By Dr Ignacio Chá ez Rivera, Facultad Nacional de Medicina de México Universidad Nacional Autónoma de México W th the collaboration of Dr Francisco Escobedo Dr Jesus Alc la Dr Salvador Franc Brow der Dr Fulvio I leggi nd Dr Mario Giordano G Mexico City 1966 Imprenta Universi taria Universidad Nacional Autónoma de México 412 pages

This book is primarily directed to the medical stu dent but it is sufficiently comprehensive to be read w th profit by the practicing physician and cardiologist The first section of the book de voted primarily to problem related to coma, is concise and w ll wri ten However it is n the subsequent sections on shock syncope, and car diac arrest that the thor excels Considerable emphasis is placed on pathologic physiology and pecific details of therapy are given relatively superfic ial coverage The basic concepts of l nical renal nd ardiovascular ph siology are pre sented in lear and elegant language There is an extensive bibliography which ma y papers from the Mexic n literature are cited in addition to the contributions of English nd Europe n workers Numberous tables nd diagrams add onsiderably t the educational value of this book

THE HEART D C CULATION IN THE NEWBOR AND INFANT Ed ted by Donald F Cassels, M D New York, 1966, Grune & Str t on Inc 426 pages Price $9 50

This is the proceed ngs of n international sympo sium on the heart nd irculation in the newborn and inf t held several month go (the dat is not indicated) nder the uspices of the Chicago Heart Association. The subjec discussed are the physiology of the fetal circulation physiologic d ju tment in the newborn, hemodynamic nd bio hemical bnormalities in the newborn with heart disease pathology of the heart in the transition period electrocardiography nd surgery of the heart and gre t essels in the first 6 months of lif There are many rather short papers, w th a dis cussion following the present tion of ach group of papers on the subject listed abov These presentations summarize the opinion of the uthors. At times these are so brief that the reader is left wondering bout the evidence f r some of the conclusions An example of this sort of brevity is obviou in the discussion of vector cardiography on page 312, the result of surgery on page 3.1 and the surv al of operated patient referred t on page 324 The reader will find the book interesting and typical of published pro ceedings of symposia

DIFFERENTIAL DIAGNOSIS OF CONGENITAL HE RT DISEASE By Nikolaus Schad M D Ralph K nzler M D nd Teoman Onat M D New York 1966, Grune & Stratton Inc 454 pages Price $29 75

This i well-illustrated and rather detailed dis cussion of the diagnostic char cteristics of nd the differential diagnostic problems related to, *congenital heart disease The authors described* the linical as w ll as the roentgenographic elec trocardiographic, nd phonocardiographic ma i festations of ongen tal he rt disease in order to correlat these i the diagnosis of the defects This is w ll done However the reader will find the presentations, which are based upon discus sion of specific cases difficult t follow t times There is good bibliography ppended t the book I general, the book ha the format of tla It is good book which cont ins consider ble amount of very unusual l ic l material

Books received

A TIVITAMINS-ANTIVITAMINE Edited by J C Somo g i Basel 1966 S Karger 231 pages Price $17 60

BRITISH PIONEERS IN THE STUDY OF HE T DISEASE B H ley Williams, London 1966, Chest nd Heart Association 16 pages

DE CONCEPT DE LA C NJONCTION DE L AIR ET DE S O D N LE POUMON By Andre Cournand Stutt gart 1966, Verlag H ns Huberbern 46 pages

FORTSCH ITTE DER ELEKTROKARDIOLOGIE 1963 1964 By G I Lempert Wien 1966, Springer Verlag 287 pages Price $11

IT ALL ST RTED WITH HIPPOCR TE By Richard Armour New York 1966, McGraw Hill Book Co. Inc

Y R COME BACK By William B Walsh New York 1966 E P Dutton & Co., Inc 192 pages Price $4 95

PHYSICI B IC I DEX Issue No. 6, J ly 1966, Kettering Ohio 1966, Charles F K ttering Memo rial Hospital, 132 pages Price $2 per month

Obituary

Robert Purves Grant

On Aug 16 1966 Dr Robert Purves Grant died suddenly and unexpectedly at the age of 50 His death was due to coronary artery disease the disease which was to have been the chief target of his efforts in his new role as Director of the National Heart Institute A Memorial Service was held in Bethesda Maryland on Sept 9 1966 In this simple moving ceremony attended by many of his friends and colleagues, his qualities and virtues were recalled by his old friend Dr Carlton B Chapman.

Bob Grant was born in Ontario Canada on Sept. 17 1915 His undergraduate and medical education were at Cornell where he received his M D degree in 1940 He served an internship and assistant residency at the Peter Bent Brigham Hospital in Boston and entered the Army Medical Corps in 1942. He was a Research Associate at Tulane in 1947 then joined the faculty of Emory University School of Medicine as head of the Cardiology Unit at Grady Hospital He joined the National Heart Institute in 1950 as Chief of the Section on Cardiodynamics, a position which he held until 1959 when he became Chief of the Training Grants and Fellowships Section In 1961 and 1962 he was Visiting Professor at several European universities during the tenure of a Commonwealth Fund fellowship. He remained in Europe as Assistant Chief and then as Chief of the N I H European Office in Paris. He was called back to the United States early in 1966 to become Director of the National Heart Institute the position which he held from March 8 1966, until his death

The above mentioned facts are the raw data which trace his career but all who knew him will rebel at the thought that thus does justice to his memory His students will remember him as a superb teacher with the rare ability to fit the subject matter into a pattern which unfolded with great clarity His gentleness in dealing with the imperfections and half learning of his students plus his encouragement and stimulation combined to make him a tremendously popular and effective faculty member He was always surrounded by students, in the ECG reading room in the laboratory or on the wards.



Robert Purves Grant, 1915-1966

His friends and colleagues will remember him as a man of great depth humility

sincerity and warmth He spoke quietly and seemed to be incapable of anger or intemperate outbursts. He had broad interests outside of medicine including music sculpture art and philosophy He had a deep *social conscience* which *led* him to try to better the plight of those less fortunate He was particularly troubled by racial inequities, and in a time when such activities were less acceptable he placed himself in professional and personal jeopardy by attempting to help the Negro physicians of the Atlanta area

The central theme of all his work was the myocardium its electrical activity producing the electrocardiogram its conduction system factors regulating growth and hypertrophy and the production of abnormal patterns of growth and rotation. His research seems to have been synthetic rather than divisive He sought the broad underlying principles producing order and cohesion He was fascinated by the relationship between form and function which may have been related to his artistic skills. Although he was tremendously successful as a medical author he always wrote reluctantly His papers usually went through multiple revisions over one or two years *before being sent to an editor* He always did his own illustrations, which were revised as often as was the written material These traits may account for the fact that his bibliography is not outstanding in its length His writing does contain many new insights and directions often in areas considered to be *thoroughly* covered and settled

The selection of Bob Grant as Director of the National Heart Institute was widely acclaimed He had exactly the right combination of personal qualities, scientific qualifications and concern for people He could attract capable men could mold *scientific effort into a plan of action with*out threatening or destroying and could plan realistically on a sound background of knowledge and experience He had just begun his work selecting as his first objective a reduction in the mortality caused by coronary artery disease and myocardial infarction His death tragically underlines *the wisdom of his choice His personal* efforts had already attracted an array of ability and interest and his plans will undoubtedly be carried forth but it is hard for us who have known him to see how his personal touch can be spared

E. Harvey Estes Jr M.D
Duke University Medical Center
Durham N C

American Heart Journal

February 1967 Volume 73 Number 2

Editorial

Alcoholic lung disease—An hypothesis

George E. Burch M.D.
Nicholas P. DePasquale M.D.
New Orleans, La.

The high incidence of pulmonary emphysema, pulmonary fibrosis, and/or bronchiectasis in alcoholics leads to the impression that chronic lung disease is endemic in these people. Clinicians are usually satisfied to explain chronic lung disease in alcoholics on the basis of poor nutrition, frequent infections of the respiratory tract, aspiration pneumonitis, and excessive smoking. There is no doubt that these factors contribute significantly to the high incidence of chronic lung disease in alcoholics. However, it is interesting to speculate that alcohol itself may produce pulmonary damage.

It is generally believed that alcohol is eliminated from the lungs passively during expiration. However, experimental studies have shown that ethanol metabolites are fixed in pulmonary tissue and that unmetabolized alcohol reaches the lungs.[1] Furthermore, Masoro, Abramovitch, and Birchard[2] have found that rat lung tissue is capable of completely oxidizing alcohol and of utilizing alcohol in the synthesis of fatty acids. In general, clinicians have ignored the metabolic abilities of pulmonary tissue and we are unaware of any metabolic pulmonary disease.

After it is ingested, alcohol goes first to the liver and then to the parenchyma of the lungs. Thus, the delicate tissues of the lungs receive all of the alcohol that is not immediately fixed by the liver. In the chronic alcoholic, the concentration of alcohol that reaches the lungs may be considerable. Then, either by direct toxicity (e.g., denaturation of proteins) or by interference with metabolic processes, alcohol may produce cellular injury. The fact that the cells may already be injured by infection and/or cigarette smoking may render them even more vulnerable to injury by alcohol.

There is fairly reliable evidence that alcohol may produce heart muscle disease independent of nutritional factors. Inasmuch as the lungs receive a higher concentration of alcohol than does the heart, it is not unreasonable to assume that the lungs may also be injured by alcohol independent of other factors.

The hypothesis that the ingestion of alcohol may produce clinical pulmonary disease is extremely difficult to establish. However, preliminary studies conducted in this laboratory have demonstrated histochemical alterations in the lungs of mice that received intraperitoneal injections of alco-

Received for publication June 2[illegible], 1966.
*Department of Medicine, Tulane University School of Medicine, [illegible]430 Tulane Ave., New Orleans, La. 70[illegible]2.

hol It would be interesting to study the incidence of pulmonary disease in alcoholics who are nonsmokers. Unfortunately it is a rare alcoholic who does not smoke Nevertheless, we would like to suggest that the frequent association of alcoholism and pulmonary disease is due at least in part to direct damage of lung tissue by alcohol

REFERENCES

1 Casier H Accumulation of alcohol metabolites i the form of total lipids and f tty acids i the organism, Quart. J Stud Alcohol 23:529 1962
2. Masoro, E. J Abramovitch H and Birchard J R Metabolism of C^{14}-ethanol by surviving rat tissue, Am. J Physiol. 173:37 1953.

Clinical communications

Pheochromocytoma masquerading as overwhelming infection

Herbert L. Fred, M.D.
David P. Allred, M.D.
Harold E. Garber, M.D.
Klaus Retiene, M.D.
Harry Lipscomb, M.D.
Houston, Tex.

Pheochromocytoma properly has been termed the great mimic. This tumor has masqueraded chiefly as essential[1] or malignant[2] hypertension, diabetes mellitus, thyrotoxicosis, or various types of neurosis. Occasionally its manifestations have been mistaken for those of gastrointestinal bleeding,[7] myocardial infarction, abdominal catastrophies, gallstone colic, cerebral tumor, primary renal disease, acute adrenal insufficiency, toxemia of pregnancy, acute pancreatitis, carcinoid syndrome, acute porphyria, pulmonary embolus, abdominal or idiopathic epilepsy, tetany, or cranial arteritis.

The case to be reported is that of a woman whose terminal illness we attributed clinically to overwhelming bacterial infection. Proof of infection, however, never was obtained. More importantly, necropsy disclosed an unsuspected pheochromocytoma. In this communication we shall present evidence to support our belief that the tumor was responsible for the clinical features observed.

Case report

A 62-year-old Caucasian woman was brought to the hospital on March 7, 1965, because of stupor. During the preceding 10 years she had been treated intermittently for diabetes mellitus and hypertension, but details of these illnesses were not available. The patient apparently had been asymptomatic until 4 days before admission, when she began to have abdominal discomfort and vomiting, especially after eating. At about the same time she experienced feverishness and nonproductive cough. Approximately 6 hours before admission she became weak and hyperactive. Her physician administered 20 mg. of prochlorperazine (Compazine) orally and 25 mg. of chlorpromazine (Thorazine) rectally, but her clinical status rapidly deteriorated and she was referred to the hospital.

Physical examination revealed a semicomatose, restless, slightly obese woman who was sweating profusely about the face and trunk. She breathed deeply at a rate of 32 per minute and had a rectal temperature of 103.4°F., a pulse of 140 regular beats per minute, and a blood pressure of 70/0 mm. Hg. Her face was flushed, but her arms and legs were cold and cyanotic. There were râles posteriorly over the lower portion of the right lung. The abdomen was distended but soft, and the bowel sounds were absent.

The initial hematocrit value was 53 per cent; 4 days later it was 46 per cent, at which level it

From the Departments of Medicine, Pathology, and Physiology, Baylor University College of Medicine, and Ben Taub General Hospital, Houston, Tex.

This study was supported in part by Grant No. AM-04122 from the United States Public Health Service, National Institutes of Health, Grant No. 9-2123 from the National Aeronautics and Space Administration, and Grant No. HE-4444 from the United States Public Health Service.

Received for publication Feb. 21, 1966.

Address: Department of Medicine, Baylor University College of Medicine, Texas Medical Center, Houston, Tex.

remained throughout the hospital course Multiple total leukocyte count ranged between 14,500 and 23,600 per cubic millimeter with differential counts a eraging 80 per cent polymorphonuclear leukocytes, 5 per cent juvenile forms, and 15 per cent lymphocytes. On a smear of the peripheral blood the erythrocytes were normocytic and normochromic nd the plat lets ppeared to be present in adequate umbers. Urinalyses showed pH of 6.0 specific gra ty ranging between 1 011 and 1 024 a 1+ rea tion for protein and a negative to 3+ reaction for sugar the spu urinary sediments contained 5 to 8 erythrocytes and 0 to 3 leukocytes per high-power field A tool specimen was guaia negati

At the time of the patient admission the concentration of blood urea nitrogen (BUN) was 86 mg /100 ml blood glucose 300 mg./100 ml serum CO_2, 20 mEq /L sodium 130 mEq /L. chloride 84 mEq /L and potassium, 2.6 mEq /L. Two days later the BUN had fallen to 40 mg /100 ml. the serum electrolyte lues were within normal limits nd tudies of the arterial blood revealed a pH of 7.49 P_{CO_2} of 31 mm Hg a P_{O_2} of 59 mm. Hg and an O_2 saturation of 91 per cent. Three days after admission, the BUN was 27 mg /100 ml.

Roentgenograms of the chest radioisotopic scan of the lungs, nd an excretory urogram were normal Plain abdominal roentgenograms showed gaseous distention of the small and large bowel. Bronchoscopy on the second hospital day disclosed no abnormality Serial electrocardiograms revealed sinus tachycardia and nonspecific S-T and T-wave changes. Conventional tudies of the cerebrospinal fluid gave normal results. No growth of org nism ppeared in thirteen blood cultures, two urine cultures, one stool culture one cerebrospinal fluid culture and tracheal w shings.

The initial clinical impression was gram-negative bacteremia. Because of the tachypnea hyperpnea and fever multiple pulmonary emboli and bacterial pneumonia were other diagnostic consider tions. The ele ted hematocrit value and history of recent omiting suggested that the patient also was significantly dehydrated

Therapy instituted shortly after the patient admission consisted of physiologic saline, metaraminol (Aramine) tetracycline streptomycin nd penicillin Within 4 hours the blood pressure rose to 120/75 mm. Hg and use of the vasopressor was discontinued During the first 2 hospital days, 12 L. of physiologic saline and 3 L. of 5 per cent dextrose in w ter were administered intravenously the total urine output being 3 L.

Twenty-four hours after admission t a time when the patient had received 9 L. of fluid intra enously nd had shown clinical improvement her rectal temperature rose bruptly to 106.6°F Concomitantly her pulse rate increased to 160 regular beats per minute her blood pressure rose t 160/100 mm. Hg and her respiratory rate increased t 32 per minu te. Wet sponges were applied to the skin nd aspirin suppositories were administered Promptly

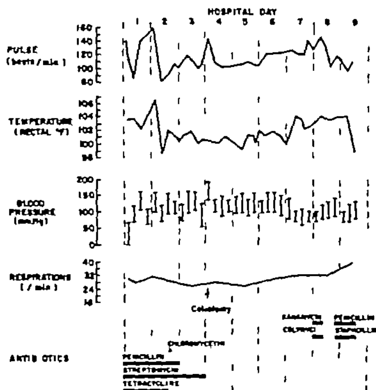


Fig 1 Pertinent linical nd therapeutic data.

thereafter her temperature fell to 98.6°F. A short time later her blood pressure dropped to 120/70 mm. Hg but her temperature rose again and remained elevated throughout the hospital course (Fig. 1).

During the third hospital day the patient's abdomen rapidly became more distended. Examination revealed a large tender cystic mass in the right lower quadrant. Because plain abdominal roentgenograms and barium enema examination suggested cecal volvulus, celiotomy was performed early on the fourth hospital day. This procedure disclosed neither volvulus nor other mechanical obstruction. An extremely dilated cecum was decompressed and five tears in its serosa were imbricated. The surgeon stated that both kidneys and adrenal glands were normal to palpation. Although the patient withstood the entire procedure well, review of the operative record showed that during an apparently uneventful induction of anesthesia with thiopental sodium a transient rise in blood pressure from normotensive levels to 190/130 mm. Hg had been recorded.

Postoperatively the patient continued to exhibit fever, tachypnea, tachycardia, ileus, and leukocytosis. Three days after celiotomy a Grade 1/6 precordial systolic ejection murmur became audible for the first time. It was heard best at the left sternal border in the fourth intercostal space. Within 24 hours the murmur increased in intensity to Grade 3/6 and bacterial endocarditis was suspected. Therefore large doses of penicillin and methicillin (Staphcillin) were administered but the patient died on the ninth hospital day.

At necropsy performed 6 hours after death, the only significant finding was an enlarged right adrenal gland weighing 30 grams. Its cut surface showed a gray-white medullary tumor surrounded by cortical remnants. Part of the gland was covered with Zenker solution and the tumor, the medulla, turned a mahogany color indicating the presence of catecholamines.[19] Histologically, the cortex was normal and distinct from the adjacent neoplastic tissue. The tumor cells were pleomorphic and ranged in size from 10 to 60μ. Their cytoplasm was abundant and had uniformly fine granules which gave a positive reaction to Gomori chromaffin stain. Foci of hemorrhage and necrosis were present in the vascular stroma. An oil red O stain for neutral fat was positive in the cortex but not in the adjacent tumor. These histologic and histochemical findings were considered to be typical of pheochromocytoma.

The tumor was assayed biologically and chemically. Acid-saline tissue extracts were brought to concentrations of 0.1 mg., 0.5 mg., and 1.0 mg. of tissue per 0.2 ml. of solvent. The increase in arterial blood pressure of pithed rats was used as a measure of pressor activity. Unknowns were assayed against standards of 0.0001 mg., 0.0005 mg., and 0.001 mg. of l-epinephrine. An epinephrine content of 0.6 mg. per gram of tumor tissue was calculated in 3 six-point biologic assays.

Chemical analysis of the tissue extract using ethylenediamine revealed a fluorescing reaction product identical in behavior to that of authentic l-epinephrine. The calculated concentration of this product, presumably epinephrine, was 0.6 mg. per gram of tumor tissue. No norepinephrine was found in the extract. Although the concentration of epinephrine in this pheochromocytoma was not abnormally high, the tumor's secretory potential is attested to by the fact that the net amount of these containing epinephrine was ten to twenty times the normal.

Discussion

There is strong support for our belief that the tumor in this patient was responsible for the clinical features observed. First, the history of hypertension[2,3] and diabetes mellitus[4] is consistent with a functioning pheochromocytoma. Second, abdominal pain, nausea, and vomiting are frequent manifestations of this tumor.[21] Third, a pronounced sensitivity to the hypotensive effects of phenothiazines has been observed in patients with this neoplasm.[11,22] Fourth, patients with pheochromocytoma are known to exhibit various combinations of fever,[22] spontaneous hypotension,[23,24,25] tachycardia,[23,27] tachypnea,[9,24] flushed facies,[1,24] sweating,[23-25] paralytic ileus,[9,28] and leukocytosis. Fifth, hypertension developed transiently during induction of anesthesia.[29] Sixth, extensive antemortem investigation produced no proof of infection. Seventh, the pheochromocytoma was the only significant finding at a carefully performed necropsy.

Finally, there is at least one other case of pheochromocytoma strikingly similar to ours in which the presenting manifestations initially were attributed to overwhelming infection. Hamrin[30] described an acutely ill 54-year-old woman with epigastric cramps, vomiting, fever, tachycardia, leukocytosis, azotemia, an elevated hemoglobin value, and a blood pressure of 130/90 mm. Hg. Less than 2 days later her temperature rose to 104.9°F. and she developed profound shock. The presumptive diagnosis was sepsis. After treatment with norepinephrine, hydrocortisone, and antibiotics, her clinical status promptly improved. During the next 24 hours 3,000 ml. of glucose and 4,000 ml. of saline solution were administered intravenously. Subsequently a slightly tender mass, thought at first to represent a perinephric abscess,

*In surgically removed adrenals from [illegible] patients with carcinoma of the prostate, from 3 with carcinoma of the breast, and from 4 with hypertension of [illegible] cause, Von Euler, Franksson and Hellström[20] found the average epinephrine content to be .49 mg. per gram and the norepinephrine content to be .09 mg. per gram.

Table I The effects of catecholamines on various organ systems in man

Organ system	Epinephrine			Norepinephrine		
	Effect	*Proposed receptor*	*Sign*	*Effect*	*Proposed receptor*	*Sign*
Heart[36,37]						
Rate	↑	β	Tachycardia	↓	Baroreceptors	Reflex bradycardia
Strength of contraction	↑	β		↑	β	
Output	↑			↑ 0 or ↓		
Blood pressure[36,37]						
Systolic	↑	β*		↑	α	
Diastolic	↓	β		↑	α	
Mean arterial pressure	0 or ↓			↑		Systemic hypertension
Peripheral resistance (total)	↓	β	Hypotension	↑	α	Peripheral and visceral ischemia
Respiration[38]						
Rate	↑		Tachypnea	↑		Tachypnea
Depth	↑		Hyperpnea	↑		Hyperpnea
Miscellaneous						
Intestinal tonus[39]	↓	α and β	Paralytic ileus	↓	α and β	Paralytic ileus
Glycogenolysis[37]	↑		Hyperglycemia			
Calorigenic action[37]	↑		Fever			
Leukocytes[40]	↑		Leukocytosis			
Sweat gland activity	↑		Hyperhidrosis			

1 the heart

was palpated in the upper region of her right kidney Further studies showed that the mass was a pheochromocytoma which secreted epinephrine predominantly The tumor was removed and the patient's symptoms subsided

The features suggesting infection in Hamrin's patient and in our patient can be attributed partly or entirely to epinephrine. In this regard the receptor theory proposed by Ahlquist[41] and modified by Furchgott[42] is helpful in understanding the systemic effects of epinephrine and norepinephrine According to this theory cells have specific receptors, possibly enzymes that interact with a catecholamine to produce a given response (Table I) This classification proposes alpha (α) receptors for contraction of smooth muscle beta (β) receptors for relaxation of smooth muscle and for increased rate and strength of cardiac contraction and a combination of alpha and beta receptors for inhibition of contraction of intestinal smooth muscle [8] In general norepinephrine stimulates alpha receptors and epinephrine stimulates beta receptors however each hormone activates both receptor sites to varying degrees.

Some of the findings in the present case deserve special comment The hypotension undoubtedly resulted from hypovolemia brought about by recurrent vomiting and sequestered fluid in the bowel lumen There also may have been an extravasation of plasma into the interstitial space as a consequence of epinephrine-induced dilatation of precapillary vessels and constriction of postcapillary vessels. The patient's subsequent toleration of massive replacement of fluid supports the contention that her intravascular compartment initially was contracted Possibly the phenothiazines aggravated the hypotension Since these drugs block alpha receptor (vasoconstrictor) activity [43] the administration of them to a patient with a predominantly epinephrine-secreting pheochromocytoma would leave beta receptor (vasodilator) stimulation unopposed and shock could supervene

Mild elevations in body temperature are common in patients with pheochromo-

cytoma[18] and temperatures as high as 107°F have been cited in some cases.[24, 42] Epinephrine acts in two ways to elevate body temperature. It increases the production of heat by augmenting cellular metabolism[44] and it decreases the dissipation of heat by producing intense cutaneous vasoconstriction.[45] Such vasoconstriction is ascribed to an effect of this hormone on alpha receptors. It is unlikely that a deficit in fluid volume per se was a major cause of fever in our patient, since she remained febrile after rehydration.

The mechanism of the heart murmur remains speculative, especially since no cardiac abnormalities were disclosed at necropsy. Accounts have been recorded, however, of loud apical pulmonic[11, 20] or aortic[46] systolic murmurs and/or soft, diastolic[8, 47] murmurs that appeared in patients with pheochromocytoma either during[20] or shortly after[46] symptomatic paroxysms. Necropsy in one of these cases and right heart catheterization and pulmonary angiograms in another[13] failed to reveal a cause for the murmur(s).

Most pheochromocytomas secrete either norepinephrine or a combination of norepinephrine and epinephrine.[48] In the latter circumstance norepinephrine usually predominates.[49] By contrast, pheochromocytomas secreting only epinephrine are rare.[50] Since the content of cathecholamines in the adrenal gland may diminish rapidly after death[42] we cannot exclude the possibility that the tumor in our patient also contained norepinephrine. Nevertheless, the results of the analysis are consistent with most of the clinical features observed.

Summary

A patient is described who had fever, hypotension, tachypnea, hyperpnea, tachycardia, sweating, flushed facies, and leukocytosis. Her hypotension responded to the replacement of fluid, but the other clinical abnormalities persisted and were accompanied later by paralytic ileus, higher fever, and the development of a precordial systolic ejection murmur of progressively greater intensity. The clinical impression initially was gram-negative bacteremia and finally bacterial endocarditis. Antemortem proof of infection, however, never was obtained. At necropsy the only significant finding was an unsuspected pheochromocytoma containing epinephrine. Evidence is presented to support the contention that the tumor was responsible for the clinical features observed.

Dr. Darryl M. Williams and Dr. Guillermo A. Nottebohm helped in the management of this patient.

REFERENCES

1. De Courcy, J. L.: Pheochromocytoma, Am. J. Surg. 86:37, 1953.
2. Goldenberg, M., Serlin, I., Edwards, T., and Rapport, M. M.: Chemical screening methods for the diagnosis of pheochromocytoma. I. Norepinephrine and epinephrine in human urine, Am. J. Med. 16:310, 1954.
3. Palmer, R. S., and Castleman, B.: Paraganglioma (chromaffinoma, pheochromocytoma) of the adrenal gland simulating malignant hypertension. Report of a case, New England J. Med. 219:793, 1938.
4. Freedman, P., Moulton, R., Rosenheim, M. L., Spencer, A. G., and Willoughby, D. A.: Phaeochromocytoma, diabetes, and glycosuria, Quart. J. Med. 27:307, 1958.
5. Ettersvelt, W., Allen, L., and Moser, M.: Pheochromocytoma with radioactive iodine uptake and electrocardiographic abnormalities. Case report with a review of thyroid-adrenal medullary interrelationships, Metabolism 11:589, 1962.
6. Crede, R. H., and Kerr, W. J.: Pheochromocytoma. Report of a case with symptoms simulating acute anxiety attacks, Postgrad. Med. 11:288, 1952.
7. Visick, J. H.: Phaeochromocytoma presenting as postural hypotension, Proc. Roy. Soc. Med. 57:673, 1964.
8. French, C., and Campagna, F. A.: Pheochromocytoma with shock, marked leukocytosis, and unusual electrocardiograms. Case report and review of the literature, Ann. Int. Med. 55:127, 1961.
9. Jelliffe, R. S.: Phaeochromocytoma presenting as a cardiac and abdominal catastrophe, Brit. M. J. 2:76, 1952.
10. Gilliland, I. C., and Daniel, O.: Phaeochromocytoma presenting as an abdominal emergency, Brit. M. J. 2:275, 1951.
11. Leather, H. M., Shaw, D. B., Cates, J. E., and Walker, R. M.: Six cases of phaeochromocytoma with unusual clinical manifestations, Brit. M. J. 1:1373, 1962.
12. Boughton, C. R.: Phaeochromocytoma. Report of a case with interesting aspects, Med. J. Australia 2:421, 1960.
13. Peelen, J. W., and De Groat, A.: Pheochromocytoma complicated by pregnancy, Am. J. Obst. & Gynec. 69:1054, 1955.
14. Lund-Johansen, P.: Shock after administration of phenothiazines in patients with pheochromocytoma, Acta Med. Scandinav. 172:525, 1962.
15. Richmond, J., Frazer, S. C., and Millar, D. R.: Paroxysmal hypotension due to an adrenaline-

secret ng phaeochromocytoma, Lancet 2:904 1961

16. Mortell, F J nd Whittle J P Pheochromocytom Case report th certain observations on the pathologic ph siology J Clin. Endocrinol 5:396 1945
17. Sack H and Koll J Cited by Hamri **
18. McG ll, R. J and D vies, J A H Phaeochromoc toma, Brit. M J 1 1698, 1962
19. Sherw n R I Histopathology of pheochromocytoma, Cancer 12:861 1959
20. Von E ler U S Franksson, C nd Hellstrom J Adrenaline nd noradrenaline content of surgicall removed h man suprarenal glands, Act Phy iol Scandinav 31:6 1954
21. Haberma F T Millheiser P J and Costen, D F Pheochromocytoma in the organ of Zuckerkandl presenting with gastrointestinal ymptoms, J Clin. Endocrinol 24:334 1964
22. B od I A Shock fter administration of prochlorperazine in patie t w th pheochromocytoma. Report of case with spontaneous t mor destruction J.A.M.A 169 1749 1959
23. Smithwick, R H Greer W E R Robertson, C W nd Williams, R W Pheoch omocytoma. A disc ssion of ymptoms, signs and procedures of diagnostic alue New England J Med 242:252, 1950.
24. Ramsay I D and Langlands, J H M Phaeochromocytoma with h potension nd poly cythaemia I ncet 2 126 1962
25. H mri B Sust ned hypotension and shock due t n adrenaline-secreting phaeochromocytoma, Lancet 2 123, 1962
26. Kahn, M T nd M Bon, D A Pheochromocytoma without h pertension Report of patient with acromeg ly J A M A 188 74 1964
27. D vies, D M Ross, J H Richardson, J E nd Larry Brown, A I Experience th phaeochromoc toma, Postgrad Med. J 39 337 1963.
28. Belt, A F nd Powell T O Cl ic l ma ifest tion of the chrom ffi cell tumors arising from the suprarenal medulla. Suprarenal sympathetic syndrome S rg Gynec & Obst 59:9 1934
29. Kirkendall, W M Liechty R D nd C lp, D A Diagnosis and tre tment of patient ith pheochromocytoma Experiences t Univer ty Hospitals from 1941 1964 Arch I t Med. 115:529 1965.
30. Delarue N C., and O Brien, D Pheochromocytoma An importa t type of curable h pertension A report of 11 cases and review of the literature Canad J Surg 6:259 1963.
31. Gifford, R. W Jr Kvale W F Maher F T Roth, G. M nd Priestley J T Clinical features, diagnosi and treatment of pheochromocytoma A review of 76 cases, Proc. M yo Clin 39:281 1964
32. Hughes, I E Bolt, D F and Hobson Q J G : *Phaeochromocytoma Presenting* resista t intestinal ileus, Proc Roy Soc Med 55:998 1962.
33. Crockett, K. A., Snow E., and Rees A L: Pheochromocytomas cause of unexpected operating room deaths, Am. Surg 27:395 1961
34. Ahlq ist R P A study of the adrenotrophic receptors, Am J Physiol. 153:586 1948.
35. Furchgott, R F The receptors for epinephrine nd norepinephrine (adrenergic receptors) Pharmacol R 11:429 1959
36. Ginsburg J and Cobbold, A F Effect of adrenaline noradrenaline nd isopropylnoradrenaline in man, *in* Wolstenholme G. E. W and O Connor M Ciba Foundation Symposium. Adrenergic mechanisms, Boston 1960, Little Brow nd Co. pp. 173-189
37. J nes, J R nd Nickerson M : *Drug acting* on postganglionic adrenergic nerv endings and structures innerv ted by them (sympathomimetic drugs) Goodma and Gilman ** pp 477 520.
38. Whelan, R F nd Young I M The effect of adrenaline and noradrenaline infusions on respiration n man Brit J Pharmacol. 8:98, 1953
39. Furchgott, R I Receptors for sympathomimetic mines, *in* Wolstenholme and O'Connor ** pp. 246-252.
40. Samuels, A J Primary nd secondary leukocyte changes following the intramuscula injection of epinephrine hydrochloride J Cl n. I vest 30:941 1951
41. Herma n, H nd Mornex, R. H ma tumours secreting thecholamines Clinical nd physiopathological stud of the pheochromocytomas, translated by R Crawford New York 1964 The Macmilla C pp 167 169
42. Goodma I S nd Gilman, A. The pharma ological basis of therapeutics, ed 3 New York 1965 The Macmilla Co p. 171
43. Howard, J F nd Barker W H I roxysmal hypertension nd other linik l m. ifest tions sociated with *benign hromaffi cell t mors* (phaeoch omocytoma) B ll Johns Hopkins Hosp 61:371 1937
44. Swa son, H E I terrelations bet een thy *oxin and adrenaline in the regulation of oxygen* consumption the albino rat Endocrinology 59:217 1956.
45. Engel, F L Mencher W H nd Engel C I Epinephrine shock as manifestation of pheochromocytoma of the adrenal medulla Report of case ith successf l remov l of the t mor Am J M Sc 204:649 1942.
46. Ema uel, D A Ross G G. Muveer M J nd Philpot A B J Prolonged hypotension ith fatal term nation after phentolamine (Regitine) methanesulfonate test J.A M A. 161 136, 1956.
47. Bernal, P Cited by Mackeith R Adrenalsympathetic syndrome Chromaffi tissue tumour with paroxysmal hypertension, Br t. Heart J 6 1 1944
48. Goodall, McC and Stone C. Adrenaline and noradrenaline producing t mors of the adrenal med lla and mpathetic nerves, A n. Surg 151 391 1960
49. Von Euler U S., and Ström G.: Present t tus of diagnosis and tre tment of phec hromocy toma, Circulation 15:5 1957
50. Herma nd Mornex, p. 139
51. Ibid p. 137

The possible role of hemoconcentration in the etiology of myocardial infarction

D P Stables M.B F.C.P (S.A.)
A H Rubenstein M.B M.R.C.P F.C.P (S.A.)
J Metz, M.D M.C.Path
A W Levin M.B F.C.P (S.A.)
Johannesburg South Africa

Recently Burch and DePasquale[1] have noted elevation of the venous hematocrit in both men and women with acute myocardial infarction as compared with control groups. Since whole blood viscosity bears a linear relationship to hematocrit at constant shear rates, these authors have suggested that reduction of hematocrit by regular venesection may be of value in the prophylaxis of myocardial infarction.

Subsequent reports have confirmed[3] and refuted[4-9] the earlier observations. Since none of these studies have made allowances for all of the normal variations in hematocrit, a comparison of venous hematocrit in coronary and control groups under defined conditions is reported. Estimations of red cell mass and plasma volume have been made on some of these subjects to determine which of these components is responsible for any change in hematocrit observed. The results suggest that an elevated hematocrit value may be of etiological significance in some patients with myocardial infarction.

Subjects

Fifty white men entering the Johannesburg General Hospital with a suspected diagnosis of acute myocardial infarction were examined. The series was random except that patients with cardiac failure were excluded since this is known to elevate the venous hematocrit.[10] Exclusions on the basis of other associated diseases which might affect the hematocrit were not made. For the purposes of this study a final diagnosis of recent myocardial infarction was allowed only if serial electrocardiography demonstrated a typical injury current as defined by criteria of the World Health Organization Expert Committee on Cardiovascular Diseases and Hypertension[11] or a similar pattern without the development of Q waves. Each series of electrocardiograms was read by two observers. Thirty five of the original 50 patients were thus accepted into the coronary group.

The control group consisted of 40 men admitted to hospital for planned surgery such as herniorrhaphy cholecystectomy

This study was supported by a grant from the Atomic Energy Board, Pretoria, South Africa.
Received for publication March 31 1966.
*Council for Scientific and Industrial Research Cardiopulmonary Research Unit, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa.
**Radioisotope Laboratory, South African Institute for Medical Research, Johannesburg, South Africa.

and excision of soft tissue tumors. These men were in excellent general health and denied symptoms of ischemic heart disease, peripheral vascular disease, or any disease known to affect the hematocrit. They were derived from the same socioeconomic group as the coronary subjects.

The mean age of the coronary group was 54.6 years and that of the control group was 51.9 years.

Methods

All patients were tested between 2 and 3 P.M. on one of the first 3 hospital days. Venous blood was obtained with strict attention to posture and avoidance of venous stasis. The recumbent position was adopted for at least 1 hour beforehand, and the arm used for sampling was kept at right atrial level. Compression of the vein was maintained for the briefest period compatible with successful venepuncture, and withdrawal of the sample was delayed until 30 seconds after the release of compression. The sample of blood was mixed with balanced oxalate. The hematocrit was measured in an international microhematocrit centrifuge within 1 hour after the blood had been collected. All samples were estimated in duplicate.

Estimations of red cell mass and plasma volume were performed on 15 coronary patients and 14 controls. None had detectable enlargement of the liver or spleen, and the coronary subjects were not in shock or in cardiac failure. Selection was otherwise solely dependent on the availability of these patients on days convenient to the authors. The investigations were performed between 2 and 3:30 P.M. on one of the first 3 hospital days. Five coronary subjects were tested on all 3 days in order to ensure that significant changes did not occur within this period. Red cell volume was measured with chromium 51 and plasma volume with radioiodinated human serum albumin as described previously.[11]

Results

The results of the venous hematocrit study are shown in Table I. The difference between the mean hematocrits of the two groups is significant at the 0.05 level, but if the numbers of subjects in each group with hematocrits in the higher ranges are compared, the differences are much more significant ($p = < 0.001$).

Table II shows the plasma and red cell volume results. There was no difference between the mean plasma volumes of the two groups. The mean red cell volume of the coronary group is higher than that of the controls, but the difference is not statistically significant ($p = 0.1$-0.2). Of the 7 coronary patients in this portion of the study with a venous hematocrit over 48 per cent, all but one had a plasma volume below the mean of the coronary group, while the red cell volume was below the mean in 4 and above the mean in 3.

The estimations of blood volume in the 5 coronary subjects whose tests were repeated over the first 3 hospital days showed no consistent variations.

Table I. Venous hematocrit values in the subjects studied

	Coronary	*Control*
Number of subjects	35	40
Mean age (yr.)	54.6	51.9
Range	33-78	34-74
Mean hematocrit value (ml./100 ml.)	47.8	46.07 $p = 0.05$*
Range	39-58	39-59
Number of subjects with hematocrit value over 48 per cent	51.5 (18/35)	22.5 (9/40) $p = 0.000761$†
Number of subjects with hematocrit value over 50 per cent	37 (7/35)	7.5 (3/40) $p = 0.000155$†

*U known one-sided rank test.
†Fisher exact probability test.

Table II Results of blood volume studies

Subjects	*Venous hematocrit* (%)	*Red cell volume* (ml./Kg.)	*Plasma volume* (ml./Kg.)
Coronary subjects			
1	39	20 51	35 41
2.	39	25 33	47 90
3	39	24 07	40 26
4	40	24 44	43 12
5	45	33 22	48 22
6.	46	31 14	42 26
7	46	29 44	37 45
8.	48	35 00	43 37
9	49	32 72	37 96
10.	49	26 28	36 93
11	49	25 46	34 80
12.	52	45 09	49 11
13.	52	23 69	25 11
14.	55	33 23	29 07
15.	56	30 29	28 53
Mean	46 9	30 56	35 86
Control subjects			
1	40	25 33	40 51
2.	41	24 36	45 74
3	42	27 96	46 75
4	42	25 88	43 01
5	42	24 39	35 41
6.	43	29 69	50 39
7	45	31 63	42 84
8.	45	30 13	42 51
9	46	23 01	32 26
10.	47	29 93	40 42
11	47	27 93	38 40
12.	48	32 33	42 53
13.	50	32 13	32 53
14.	54	25 65	22 50
Mean	45 1	27 89	39 70

Table III Details of previous studies of hematocrit values in patients with myocardial infarction

Authors	*Type of study*	*Posture*	*Position of arm*	*Pro-longed bed rest*	*Pre-ceding exercise*	*Time of day*	*Venous stasis*	*Dupli-cate values*
Burch and DePasquale	Retrospective	0	0	0	0	0	0	0
DePasquale and Burch	Retrospective	0	0	0	0	0	0	0
Conley et al.	Retrospective	0	0	Avoided	0	0	0	0
Voopio and Eisalo	Retrospective	0	0	Avoided	0	0	0	Yes
Mayer	Prospective	Sitting	0	Avoided	0	Morning	Avoided	0
Rosenblatt et al.	Prospective	0	0	Avoided	0	Morning	Avoided	Yes
McDonough et al.	Retrospective	0	0	Avoided	0	0	0	0

Arm used for sampling of venous blood
0 = Not specified.

Discussion

Although the number of subjects tested is relatively small it is believed that the results of this study have greater validity than those of previous observations. Of these seven publications five were based on retrospective analyses, and none made allowances for each of the normal variations in hematocrit such as diurnal fluctuation posture [1] preceding bed rest [11] and vigorous exercise[1] (Table III). The influence of posture is of particular importance since it applies not only to the body as a whole but also to the arm used for venous sampling,[12] yet in only one article[3] was the position of the subjects described. Five reports did not mention the avoidance of venous stasis during the collection of samples of blood.[1] Only Burch and DePasquale[1] used defined criteria for the diagnosis of myocardial infarction in their patients.

The results of this investigation indicate an association between high hematocrit values and myocardial infarction. To what extent this association is an etiological one is not answered by this study. Clearly this could be only one of many factors in the genesis of myocardial infarction and our data emphasize that a low hematocrit value does not necessarily offer protection. Five of the coronary subjects (14 per cent) had hematocrit values of less than 42 per cent the lower limit of normal at this altitude (5,740 feet).[19] Measurements of blood volume performed on 4 of these 5 subjects showed a decreased red cell mass in each instance. The exact role of hemoconcentration should be determined by a prospective study of the incidence of myocardial infarction in groups of subjects with high and low hematocrit values or by a controlled trial of regular venesection in the prophylaxis of myocardial infarction in patients with high hematocrit values. Even a minor role will be of particular significance since so few of the other factors concerned in the development of myocardial infarction are amenable to direct control.

The mean hematocrit value of the control group is lower than the figures previously reported as being normal for this altitude.[19,20] Variations in the ages of the populations studied is unlikely to be responsible since McDonough and associates[9] found that the tendency for hematocrit values to fall with increasing age was insignificant. It seems to be possible that disparity in posture or socioeconomic status accounts for the differences observed.

The studies of blood volume show that high hematocrit values in coronary subjects are more commonly due to a contracted plasma volume than to an increased red cell mass. Thus the term *erythrocytosis* applied to these patients by Burch and DePasquale[1] is inappropriate. Although most of our subjects had hematocrit values in the high normal range rather than in the polycythemic range an analogy may be drawn with cases of pseudopolycythemia (relative polycythemia, "benign polycythemia," Gaisböck's syndrome, chronic hemoconcentration syndrome, stress polycythemia)[21-23] in which a high incidence of hypertension and occlusive vascular disease is found.

Summary

Venous hematocrit was measured in 35 patients with acute myocardial infarction and in 40 control subjects under strictly defined conditions. A significantly greater proportion of the coronary group had high hematocrit values. Studies of blood volume showed that a reduction in plasma volume was more frequently responsible than an increase in red cell mass.

These results support the belief that elevation of the hematocrit may be a factor in the development of myocardial infarction.

We wish to thank the Director, South African Institute for Medical Research for facilities to carry out this study, Mr. D. Hart for technical assistance, and Professor D. J. du Plessis for access to control subjects.

REFERENCES

1. Burch, G. E., and DePasquale, N. P.: The hematocrit in patients with myocardial infarction, J. A. M. A. 180:63, 1962.
2. DePasquale, N. P., and Burch, G. E.: Hematocrit in women with myocardial infarction, J. A. M. A. 183:142, 1963.
3. Wells, R. E., Jr., and Merrill, E. W.: The variability of blood viscosity, Am. J. Med. 31:505, 1961.
4. Burch, G. E., and DePasquale, N. P.: Phlebotomy, Arch. Int. Med. 111:687, 1963.
5. Mayer, G. A.: Diurnal hematocrits in healthy subjects and patients with coronary heart disease, Canad. M. A. J. 91:951, 1964.

6. Conley C. L., Russell, R. P. Thomas, C. G., and Tumulty, P. A. Hematocrit values in coronary artery disease. Arch. Int. Med. 113:170, 1964.

7. Vooper, P. and Ebalo, A. Haematocrit values in men with myocardial infarction, Ann. Med. Intern. Fenn. 53:39, 1964.

8. Rosenblatt, G., Stokes, J., and Bassett, D. Whole body viscosity, haematocrit and serum lipid levels in normal subjects and patients with coronary heart disease, J. Lab. & Clin. Med. 65:202, 1965.

9. McDonough, J. R., Hames, C. G., Garrison, G. E., Stoll, S. C., Lichtman, M. A., and Hefelfinger, D. C. The relationship of hematocrit to cardiovascular states of health in the Negro and white population of Evans County, Georgia, J. Chron. Dis. 18:243, 1965.

10. Ehrenberg, S. Changes in blood viscosity, haematocrit value and fibrinogen concentration in subjects with congestive cardiac failure, Circulation 30:686, 1964.

11. Hypertension and coronary heart disease: Classification and criteria for epidemiological studies, First Report, World Health Organization Technical Report Series 168:26, 1959.

12. Hart, D. and Metz, J. The estimation of red cell volume with ^{51}Cr-labelled erythrocytes and plasma volume with radioiodinated human serum albumin, J. Clin. Path. 15:459, 1962.

13. Cranston, W. I. and Brown, W. Diurnal variation in plasma volume in normal and hypertensive subjects, Clin. S. 25:107, 1963.

14. Fawcett, J. H., and Wynn, V. Effect of posture on plasma volume and some blood constituents, J. Clin. Path. 13:304, 1960.

15. Ehrenberg, S. The effect of posture and position of the venous sampling site on the hematocrit and serum protein concentration, J. Lab. & Clin. Med. 61:753, 1963.

16. Taylor, H. L., Erickson, L., Henschel, A., and Keys, A. Effect of bed rest on blood volume of normal young men. Am. J. Physiol. 144:227, 1945.

17. Miller, P. B., Johnson, R. L., and Lamb, L. E. Effect of absolute bed rest on circulation functions, Aerospace Med. 35:1194, 1964.

18. Kaltreider, N. L., and Meneely, G. R. The effect of exercise on the volume of the blood, J. Clin. Invest. 19:627, 1940.

19. Lurie, H. L. Normal haematologic standard in an altitude of 5,740 feet, Quart. J. Exper. Physiol. 33:91, 1945.

20. Metz, J., Levin, N. W., and Hart, D. Effect of altitude on the body venous haematocrit ratio, Nature (London) 194:483, 1962.

21. Kaung, D. T. and Peterson, R. E. Relative polycythaemia or pseudopolycythaemia, Arch. Int. Med. 110:456, 1962.

22. Russell, R. P. and Conley, C. L. Benign polycythaemia: Gaisböck syndrome, Arch. Int. Med. 114:734, 1964.

23. Gaisböck, F. Die Bedeutung der Blutdruckmessung für die ärztliche Praxis, Deutsch. Arch. klin. Med. 83:363, 1905.

24. Hall, C. A. Gaisböck disease: Redefinition of an old syndrome, Arch. Int. Med. 116:4, 1965.

25. Lawrence, J. H. and Berlin, N. I. Relative polycythaemia: The polycythaemia of stress, Yale J. Biol. Med. 24:498, 1952.

Effects of posture and exertion on levels of serum cholesterol and lactic acid

L M Dalderup M D
Amsterdam Netherlands

Although the effect of posture on plasma volume protein content and the hematocrit value was known [1] and an influence on the cholesterol level was suggested years ago [2] little attention was paid to its consequences until recently [3]

In a 2 year study of the effects of physical exertion on the serum cholesterol levels difficulties were encountered since the acute effect of exertion proved to be of the same order as that induced by changes in posture Lactic acid levels were studied in addition The effects of exertion on the serum levels are reported in detail separately [4]

The effect of meals on the serum cholesterol level is small In another investigation the effect of the main (hot) meal proved to be a decrease of 1 to 2 mg per cent. Two groups of 20 male subjects were studied in succession and 16 observations over a period of a year were obtained in each group [5]

Methods

The subjects of the present study were young male prisoners 18 to 25 years of age (average of 21 years) and an older group of male prisoners up to 48 years of age (average of 29.5 years) From the younger group samples of blood were obtained under the following conditions while the subjects were in bed after waking up sitting after washing dressing and eating breakfast then after walking leisurely for 200 to 300 meters after climbing a flight of stairs (4 60 meters) and subsequently after resting for periods up to 130 minutes in various postures. With both groups, studies were made of the effect of moderate exertion with the Åstrand Ryhming[11] step test (stepping up and down a bench 40 cm high 22 5 times per minute during 5 minutes) which was started after the subject had been sitting on a chair for 30 minutes Blood for analyses was taken from an antecubital vein.

Duplicate series of measurements could occasionally be taken after days to weeks during which period a daily (5 days a week) 80-minute indoor exercise program was started or continued

On each sample of serum duplicate analyses were made for cholesterol according to Anderson and Keys,[12] and for lactic acid according to Scholz and associates

Results and discussion

The changes in the levels of cholesterol and lactic acid on changing posture whether combined or not with exertion are given in Table I The levels are lowest when the

From the Netherlands Institute of Nutrition, Wageningen, Netherland
Received for publication April 11 1966.
Address Medical Department, Netherlands Institute of Nutrition, Gerrit van der Veenstraat, 33, Amsterdam Netherlands.

Table I. Effects of changing posture walking climbing a flight of stairs and rest in various positions

	Changes in serum content with standard errors	
	Cholesterol (mg %)	*Lactic acid (mg %)*
A. From recumbent in bed to		
Sitting	+12 8 ±1 2	−0 1 ±0 6
Standing/walking	+17 4 ±1 4	+0 6 ±0 6
Walking, climbing a flight of stairs	+15 2 ±1 2	+2 1 ±0 8
Number of observations	70	26
Number of subjects participating	49	26

B From standing values to

Time spent (min)	Cholesterol (mg %): *Sitting* — Changes in respect to value downstairs	Cholesterol (mg %): *Sitting* — No step down stairs changes in respect to value upstairs	Cholesterol (mg %): *Recumbent* — Changes in respect to value downstairs	Lactic acid (mg %): *Standing* — No step down-stairs changes in respect to value upstairs	Lactic acid (mg %): *Sitting* — Changes in respect to value upstairs
0 5	−2 15	+5 4	—	+0 4	+0 8
1 5	−2 6	+1 9	—	+3 1	+1 6
2 5	−4 9	−0 1	—	+3 8	+2 5
3 5	−4 3	−3 3	+0 7	+3 8	+2 5
10	−4 0	−4 7	−6 5	+6 0	+0 9
30	−5 0	+0 3	−9 9	+8 2	−0 3
60	−8 3	−4 7	−8 0	+3 5	+0 8
90	—	—	−7 7	—	—
120	—	—	−6 5	—	—
Standard errors	±1 1 to ±1 5	±2 3 to ±5 0	±1 3 to ±2 4	±1 6 to ±2 8	±0 6 to ±1 1
Number of observations	58	9–3	21 18	8–4	27 21
Number of subject	52	9	21	8	27

*The subjects had venepuncture downstairs in sitting position, hence, the values started to decrease and did not arrive at the former high level in the short time spent [illegible] climbing the flight of stairs

subject is in the recumbent posture. After the subject had climbed a flight of stairs of 4 60 meters the level of cholesterol was lower than that recorded downstairs at the end of a 200 to 300-meter walk at ground level The three fourth minute spent sitting for the sampling of blood probably disturbed the "standing pattern.

In all 49 subjects, at least one of the levels measured while sitting after walking or after climbing stairs was higher than that found in the recumbent position and in all but 17 of these 210 observations this was the case (in 4 there was no change which is a highly significant effect

In the 43 subjects in whom direct comparison was possible sitting for 1 hour after arrival upstairs produced an average level of 11.4 mg per cent above that found while they were still in bed; averaged over all 70 available observations, including

the incomplete series a value of 9.1 mg per cent was found. These changes are not significantly different from the average increase (12.8 mg per cent) seen by comparing sitting values with those found while the subjects were recumbent in bed (Table I). The standard error of the difference was about 2 mg per cent for both differences. Some after-effect of standing toilet activities might, however, have been present in the 12.8 mg per cent value, since 130 minutes of rest in the recumbent position were not enough for the value found at waking up in bed to be reached. When the subjects rested in the standing position, a slight increase in the levels was seen, indicating that the maximum was not yet reached upon their arrival upstairs. The maximum effect was present after about 15 minutes, which is also about the time that Fawcett and Wynn[3] found to be necessary, for instance, for the maximum serum protein level to be reached in healthy subjects. The slight increase in the values in the first resting minutes after arrival upstairs in the subjects who did not stop downstairs for the taking of blood is according to expectations, since the time spent in the upright position was shorter than if blood had also been taken downstairs (after the men had awaited their turn). It is improbable that it is due to exertion, because an average increase of 7.3 mg per cent was found in 59 young subjects immediately after the Åstrand Ryhming step test in comparison to the values before the test—after 30 minutes of resting on a chair—and this is only slightly more than the difference between sitting and standing. Shorter step tests in a smaller number of participants who were bled during the exercise showed a rise in the levels of 3.7, 7.2, and 3.0 mg per cent, respectively, after 1, 3, and 5 minutes. After the daily 80 minutes of exercising, the end posture of which might vary, an increase of 4.7 mg per cent was found, averaged over 85 observations in 22 subjects of the older group (Table II).

The effect of exertion on a bicycle ergometer (load 214 watts) until exhaustion, however, produced an average rise of 14.8 mg per cent. Forty minutes of rest in the same position resulted in a level 3.8 mg per cent higher than that at the start of pedaling, which was allowed only after 15 minutes of rest in the working position (Table II). This indicates that rest periods preferably must be longer than were those chosen (arbitrarily) for this experiment.

The lactic acid levels were not dependent on posture, but the climbing of a flight of stairs produced a slight increase in the levels; this increase started to disappear after a few minutes (Table I). With the

Table II. Influence of exertion on levels of serum cholesterol and lactic acid

Exertion + posture	Number of subjects and observations		Change in cholesterol level and standard errors		Number of subjects and observations		Changes in lactic acid level with standard error	
Step test								
After 1 min.	5	9	+3.7	±2.8	—	—	—	—
After 3 min.	6	11	+7.2	±2.4		—	—	—
After 5 min.	12	23	+3.0	±2.2	—	—	—	—
Step test 5 min.	59	195	+7.3	±0.7	64	321†	+13.1	±0.5
80 Minutes indoor training	22	85	+4.7	±1.1	—	—	—	—
Exertion only, bicycle ergometer until exhaustion (2 to 18 min.)	20	35	+14.8	±1.8	20	35	+61.6	±4.2

*Same subjects.
†On [illegible] of the 321 [illegible] after the step test lower than those before, except for one; these subjects had a starting level of 21 [illegible] per cent or more, which suggests that they had not really been resting before the test. [illegible] the same subject had lower levels on other occasions.

Astrand Ryhming step test an increase of 13 1 mg per cent was found about doubling the pre-step-test level of 14 7 mg per cent ± 0 2 which however was still definitely higher than the average level of 11 6 mg per cent found at waking up. Also this difference was statistically sig n ficant the standard error of the differ ence was ± 0 8 mg per cent. With pedaling th bicycle an increase of *64 6 mg per* cent, on an average was found (Table II)

Since hydrostatic and osmotic counter action is the cause of the posture effect, a difference between the protein bound serum cholesterol and the free lactic acid could be expected The effect of posture on the serum cholesterol levels (17 4 mg per cent in the young group with an average cholesterol level of 224 mg per cent) was 8 per cent which accords well with the effects on serum protein levels, re ported to be 8 to 12 per cent by various authors. Recently Stoker and associ ates reported an effect of 12 9 per cent on the cholesterol levels, whereas this was only 6 7 per cent for the partly protein bound serum calcium Stoker and associ ates (l.c.) did not find a slow and a rapid adaptation phase n the present study the standing value was reached in about 15 m nutes, whereas the values in the re cumbent positions might take an hour or *more to obtain, which is more like the* findings of Widdowson and McCance Edema might seriously prolong the time *necessary for reaching the maximum* and especially the minimum values. The pos*ture effect is* important not only for com parisons of the levels of normal blood con stituents, but also for the levels of drugs, since a number of them is protein bound

Conclusions

When serum cholesterol levels are being measured the influence of posture should be taken into consideration Since the elevation takes only about 15 minutes to reach its maximum when the subject is standing th procedure should be recom mended an hour or more of resting in a sitting or recumbent position did not al ways prove to be long enough for the reaching of equilibrium in that posture

Since the elevation of the serum cho lesterol level by working to exhaustion is less than that due to the effect of posture and severe exhaustion will as a rule not occur when subjects come for blood exami nations the exertion factor will then be small The same is true for the effect of meals.

Serum lactic acid shows no effect due to posture but increases immediately upon slight exertion

The posture effect is limited to the non-filterable compounds of the blood and in cludes therefore the serum proteins and all substances that are protein bound the blood cells and other large particles whether foreign or not

Summary

In male prisoners, 18 to 48 years old the effects of posture were studied on the levels of serum cholesterol and serum lactic acid The effect of posture is limited to the nonfilterable elements of the blood such as the proteins and therewith also to all protein-bound serum compounds. As for these compounds, higher levels are found when measurements are made with the subject standing than when he is seated and again the values are higher in the sitting than in the recumbent position. The increase in the values when posture was changed from recumbent to standing was 8 per cent Exertion and *meals affect the cholesterol levels less than* does a change in posture. The lactic acid level is not dependent on posture but rises with slight exertion.

This study was made possible by the financial support of the Netherlands Dairy Board—we are especially indebted to Ir E A M Meyknecht by the material and practical h lp of the Ministery of Justice the Prison Governing Board nd he Medical Staff in charge especially are w indeb ed to the stimulating support of N de Vong'd M D the Medical Inspector in Chief and for technical assistance e are indeb ed A B Pappie M D nd G H M Keller Ph D

REFERENCES

1 Thompson, W O Thompson P K and Dailey M E The effect of posture upon the composition nd volume of the blood man Proc N t Acad Sc 14:94 19 8
2 Thompson W O Thompson I K and Dailey M E The effect of pos ure upon the composition and olume of the blood in man J Clin I est 5:573 1928
3. W erfield, R L The effect of posture on be

circulating blood volume J Physiol. 72 110, 1931

4. Widdowson E M and McCance R A The effect of undernutrition and of posture on the volume and composition of the body fluid Studies of undernutrition Wuppertal, 1946-1949 Medical Research Council Report N 275 p 170 1951
5. Fawcett J K and Wynn V Effects of posture on plasma volume and some blood constituents J Clin P th 13:304 1960
6. Eisenberg S Postural changes in plasma volume in hypoalbuminemia, Arch. I t Med. 112:544 1963
7. Eisenberg S and Wolf I C Plasma volume after posture change in hypertensive subjects, Arch I t Med 115 17 1965
8. Stoker D J Wynn, V and Robertson C Effect of posture on the plasma cholesterol level, Brit M J 1:336 1966
9. Dalderup L M The effect of exertion on serum cholesterol lactic acid and potassium levels, on pulse rate and on the T wave of the electrocardiogram Circulation Res J press.
10. Dalderup, L. M De Voogd, N Meijknecht, E. A. M and Den Hartog, C. The effects of increasing the daily physical activity on the serum cholesterol levels, Nutrio et dieta. In press, 1966
11. Dalderup, L. M Van der Spek, P A. F and Affourtit Leeuw H. Clinical experiences in a study on relation between dietary and serum lipids in oligophrenics (In Dutch, with a summary in English) Tijdschr voor Zwakzinnigh. en Zwakzinnigenzorg 3:61 1966.
12. Åstrand, P O and Ryhming I A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work, J Appl. Physiol. 7:218, 1954.
13. Anderson J T and Keys, A Cholesterol in serum and lipoprotein fractions Its measurement and stability Clin. Chem 2 145 1956
14. Scholz R., Schmitz, H Bücher Th and Lampen, J O Über die Wirkung von Nystatin auf Backerhefe, Biochem. Ztschr 331 71 1959

Peripheral arterial dilution curves in the appraisal of left ventricular diastolic volume

Richard P Lewis M.D
J David Bristow M.D
Herbert E. Griswold M.D
Portland Ore

In recent years, measurements of left ventricular volume have been made in man by angiographic and indicator-dilution techniques. These studies require specialized methods and equipment and it would be desirable to have a simple means to determine whether the left ventricular volume is normal or abnormal. In 1960 Jose McGaff and Milnor[1] described an analysis of systemic arterial indicator dilution curves which was shown to be especially sensitive to the volume encountered by the indicator particles between the injection and sampling sites. The authors employed this appraisal of indicator curves to judge the magnitude of aortic and mitral regurgitation. We have found that this method is also useful to distinguish a normal from an abnormal left ventricular end-diastolic volume.

Method

Left ventricular volumes were determined by the thermodilution method in 74 patients. The details of this technique as we employ it have been described previously.[2-4] The patients presented a variety of cardiac disorders, as shown in Fig 1. No one with mitral regurgitation was included because the indicator-dilution method for volume is not applicable when this lesion is present. The left ventricular end diastolic volume (EDV) was measured at rest in all. In addition 29 determinations were made during supine exercise or during the intravenous administration of isoproterenol. The average normal value for EDV determined by indicator-dilution methods is very close to 100 ml. per square meter of body surface area (ml./M.²).[2-] The upper limit of normal is below 140 ml./M.² and is probably nearer to 130. In this study 140 ml./M.² was arbitrarily chosen as the upper limit in order to identify the definitely abnormal EDV and because this figure provided the best separation of our results.

Indicator-dilution curves were obtained by left ventricular injections of 5 mg. of indocyanine green dye and brachial arterial sampling performed nearly simultaneously with the recording of the thermodilution curves. Sampling was through 34 cm. of polyethylene tubing (internal diameter of 0.113 cm.) including the section inserted percutaneously to the brachial artery. The volume of the sampling system varied from 0.4 to 0.5 ml. A Colson densi

From the Division of Cardiology, Department of Medicine, University of Oregon Medical School, Portland, Ore.
This [illegible] was supported by United States Public Health Service Program Project Grant No. HE 06336-03.
Received for publication April 11, [illegible]
Address: Department of Medicine, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Rd., Portland, Ore. 97201

tometer was used with a pump which withdrew blood from the brachial artery at a rate of 24.7 ml. per minute. Calibrations were performed by adding known amounts of the indicator to arterial blood and drawing it through the densitometer at the same flow rate as that employed during inscription of the original curves.

The cardiac output was calculated from the dye-dilution curves. They were then analyzed according to the method of Jose and associates. The peak concentration (PC) was obtained by determining the concentration of indicator (milligrams per liter of blood) at the top of the curve. This value was corrected for body size by dividing it by the dose of indicator injected per kilogram of body weight. The slope time (ST) is the time in seconds required for the exponential portion of the downslope of the curve to pass through one logarithmic cycle when replotted on semilogarithmic paper. The PC is then divided by the ST to obtain the PC/ST ratio.

Results

Fig. 1 illustrates 103 comparisons of PC/ST and EDV. The PC/ST values range from 2 to 98 and the EDV range was from 67 to 422 ml./M.² When the PC/ST exceeded 25, the EDV was below 140 ml./M.² in 54 of 56 cases. When the PC/ST was less than 25, the EDV was greater than 140 ml./M.² in 44 of 47 cases.

Fig. 1. See text.

There was no relationship between the PC/ST ratio and the cardiac index, that is, any PC/ST value could be associated with any level of cardiac index. In individuals the PC/ST ratio at rest and during exercise continued to reflect EDV in spite of considerable increases in blood flow.

Discussion

The ability of the PC/ST ratio to reflect the definitely abnormal EDV is remarkably good considering that the dilution curve from which it is measured is recorded a considerable distance away from the central aorta and left ventricle. The discrimination appears to depend on the fact that the PC is sensitive to the dilution volume encountered by the indicator and the ST is related to both the dilution volume and the cardiac output. Thus, the PC/ST is more powerfully related to dilution volume and less affected by the flow rate. This contention was confirmed by comparisons of rest and exercise values.

Studies with experimental models indicate that the largest mixing chamber encountered by the indicator particles will dominate the shape of an indicator-dilution curve.[4] In most individuals this chamber is the left ventricle when the indicator is injected into the left side of the heart and sampled from a peripheral artery. When mitral valve disease is present, however, the volume of the left atrium may exceed that of the left ventricle and curves obtained from injection into the left atrium may differ from those from the left ventricle. Consequently, it is probably important to employ left ventricular injections to use PC/ST for appraisal of LDV in patients with mitral stenosis. In most individuals with isolated aortic valve disease, arterial dilution curves do not differ significantly whether the injection is left atrial or left ventricular. In some with aortic valve disease, however, there may be marked poststenotic dilatation and it is possible that the ascending aorta could become the largest mixing chamber. Two of the patients with abnormal PC/ST ratio and a normal EDV in our group had marked poststenotic dilatation.

All but two of the patients with an abnormal PC/ST had some degree of aortic

regurgitation. In these instances there were two factors which could have produced an increase in the dilution volume to which the indicator was exposed First, the EDV was elevated Second the regurgitant flow itself probably acted to increase the effective dilution volume. It might be expected that a patient with an increased EDV without a regurgitant lesion might have less deformity of the indicator curve than a person with a similar EDV who also had a regurgitant lesion. We have little information in that type of patient. It is important to note, however that in patients with regurgitant lesions the PC/ST was normal if EDV was normal

Whether the PC/ST is useful in the evaluation of EDV in patients with mitral regurgitation must remain speculative since some indicator may be trapped in the left atrium in instances of this lesion, and because we have not been able to test the thesis by using an indicator-dilution method for the estimation of ventricular volume. Of interest, we have noted a normal PC/ST ratio from curves from left ventricular injection in patients with mitral regurgitation in whom angiography suggested a normal or nearly normal left ventricular EDV

The present studies do not bear upon the problem of finding the most accurate method for determination of left ventricular volume. Rather the comparisons demonstrate certain interrelationships between indicator-dilution curves of high fidelity recorded at the aortic root (thermodilution curves) the stroke volume, and the configuration of dilution curves recorded at some distance downstream from the left ventricle (PC/ST ratio) The correlations were better than had been expected and provide, we believe, additional usefulness for dye-dilution curves recorded from peripheral arteries.

Summary and conclusions

A method is presented for discriminating between a normal and abnormal left ventricular end-diastolic volume, based on the configuration of indicator-dilution curves recorded from peripheral arteries. The analysis appears to be useful in a variety of cardiac lesions although further work is required to determine its applicability in mitral regurgitation Although not a substitute for direct estimation of left ventricular volume, the measurement is simple and is suggested as a useful adjunct to other studies during cardiac catheterization.

REFERENCES

1. Jose, A. B., McGaff C J and Milnor W The value of injections of dye i t the left heart in the study of mitral and aortic valvular disease by catheterization of the left heart, Am. Heart J 60:408, 1960.
2. Rapaport, E., Wiegand, B. D and Bristow J D The estimation of left ventricular residual volume in the dog by thermodilution method, Circulation Res 11:803 1962
3. Bristow J D Crislip, R L., Farrehi, C. Harris, W E., Lewis, R. P Sutherland, D W and Griswold H. E. Left ventricular volume measurements in man by thermodilution J Clin. Invest 43:1015 1964.
4 Lewis, R. P Bristow J D Farrehi, C Kloster F E. and Griswold, H. E. Idiopathic left ventricular hypertrophy A hemodynamic reappraisal, Am. J Med. 38:842, 1965.
5 Gorlin, R Rolett, E. L., Yurchak, P M., and Elliott, W C. Left ventricular volume in man measured by thermodilution, J Clin. Invest. 43 1203, 1964.
6 Paley H. W and Leonard J J The effect of exercise in the supine posture on left ventricular performance in normal man, Clin. Res. 13 122, 1965 (abstract)
7 Folse, R., and Braunwald E. Determination of fraction of left ventricular volume ejected per beat and of ventricular end-diastolic and residual volumes. Experimental and clinical observation with a precordial dilution technic, Circulation 25:674, 1962.
8. Newman, E. V Merrell, M., Genecin, A., Monge, C Milnor W R., and McKeever W P The dye dilution method for describing the central circulation. An analysis of the factors shaping the time-concentration curves, Circulation 4:735 1951
9 Warner H. P An analysis of the role of indicator techniques in quantitation of valvular regurgitation, Circulation Res 10:519 1962.

Apexcardiography: Use in coronary heart disease and reproducibility

William M Ginn M D
Roger W Sherman M B B Chir
W Kirby Harrison Ph.D
Benjamin M Baker M D
Baltimore Md

Movements of the chest wall caused by cardiac activity have always interested clinicians. Modern recording techniques have allowed objective and systematic study in place of more or less expert impression Apexcardiography one of several current techniques records the displacement of the apex beat in relation to the chest wall Certain changes in the configuration of the tracing have been found in patients known to have coronary heart disease (CHD) This report of our experience with the method confirms the earlier finding We have paid particular attention to discrimination between normal and diseased subjects and to reproducibility

Subjects

One hundred twenty-seven subjects predominantly white were studied History cardiovascular physical examination repeated evaluation of any complaint of chest pain a chest x ray film and a standard 12 lead electrocardiogram (ECG) were obtained in each subject. Subjects were included only if they had (1) normal heart size demonstrated by x-ray examination (except for one subject with CHD who had borderline cardiac enlargement) (2) a blood pressure not greater than 140/90 mm Hg and (3) no evidence of heart disease other than CHD

Our subjects consisted of normal controls, patients with coronary heart disease patients with angina pectoris and patients with chest pain of uncertain origin this last group had all undergone selective cine coronary arteriography by which obstructing lesions had either been demonstrated or excluded Although it would have been possible merely to contrast all those who had evidence of disease with those who had no such evidence we chose to subdivide both diseased and normal subjects according to the means by which they were defined In this way we have attempted to allow for the distinction between coronary heart disease and coronary artery disease and also between subjectively and objectively defined disease. The groupings adopted are not mutually exclusive a subject may satisfy more than one set of group criteria listed below In

From the Cardiovascular Division, Department of Medicine Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore Md
Received for publication April 11 1966
*United States Public Health Service Fellow Heart Disease Control Section.
**Address 9 East Chase St., Baltimore, Md 21202.

fact only 8 subjects appear in more than one group

The groups

GROUP A. Normal 40 men with an approximately even age distribution from 30 to 72 and an average of 48 years. Definition (1) Normal 12 lead ECG *and* (2) normal cardiovascular physical examination *and* (3) no history suggestive of circulatory dysfunction *and* (4) no history of chest pain

GROUP B Coronary heart disease 41 men with an approximately even age distribution from 30 to 72 and an average of 52 years. Definition (1) Hospital record documentation of typical myocardial infarction including ECG evidence of acute infarction 3 months or more before study (35 cases) *or* (2) occlusion of one or more major coronary branches demonstrated by selective cine coronary arteriography* (6 cases)

GROUP C. Chest pain of uncertain origin, negative cinearteriography 11 men and 10 women, with an average age of 44 years. Definition (1) No disease of the coronary arteries demonstrated by cinearteriography *and* (2) no history or ECG evidence of myocardial infarction

GROUP D Chest pain of uncertain origin positive cinearteriography 16 men and 1 woman, with a mean age of 42 years. Definition (1) Significant narrowing or occlusion of one or more major coronary arteries demonstrated by cinearteriography *and* (2) no history or ECG evidence of myocardial nfarction.

GROUP E. Angina pectoris, 16 men with an average age 51 years. Definition (1) Classic history of angina pectoris in the opinion of at least two physicians, *and* (2) no history or ECG evidence of myocardial infarction.

Equipment

Conventional 12 lead ECGs were recorded immediately before exercise. During exercise ECG monitoring was carried out every 30 seconds on a four-channel Sanborn Model 964 direct writer with a set of four precordial electrodes.

*These subjects underwent coronary arteriography by Dr. Richard Ross and his associates to elucidate the cause of chest pain or to investigate suitability for surgical therapy

The apexcardiograms (ACGs) were recorded with a Sanborn 374 pulse wave pickup. This pickup was attached to a small conical cup of approximately 2-cm diameter with a 6-inch length of plastic tubing that had a 2-mm inside diameter The over-all frequency response of the system was 1 to 35 c.p.s. with negligible distortion for the purposes used Miller and White[1] have reported on the electrical characteristics of this transducer

The ACGs were recorded on a six channel Schwarzer Model ST 6530 direct writer at a paper speed of 75 mm per second ECG Lead II was recorded routinely for timing A Sanborn Model 769 oscilloscope provided simultaneous visual display of the ACG

Methods

Recording the apexcardiogram With the subject lying on his left side the maximal left ventricular impulse was located by inspection and palpation. Frequently this could be done with the subject breathing quietly sometimes it was necessary for the breath to be held usually in full but not forced expiration. Occasionally there was no visible or palpable precordial movement from which a recognizable ACG could be recorded

The vicinity of the expected position of the apex was explored with the conical cup the first object was to obtain the maximum repetitive deflection which corresponded in rate to the simultaneously displayed ECG The size of the deflections usually varied through the respiratory cycle and the stage at which they were largest was noted Final fine adjustment was directed toward obtaining the most typical ACG with particular reference to (1) a sharp nadir (the O point) occurring after the T wave of the ECG and preferably with symmetrical limbs (2) a sharp rise (the rapid filling wave) immediately after the O point followed by a more gentle rise (the slow filling wave) on which there should be, in most cases, a positive deflection shortly before the R wave of the ECG and (3) a steep upward deflection approximately synchronous with the R wave of the ECG (Fig 1)

Tilting the cup or changing its position minimally from the chosen point could

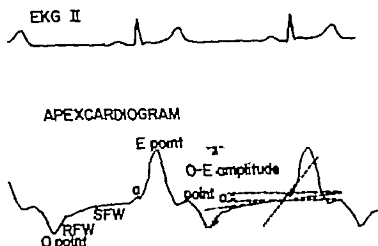


Fig 1 A normal apexcardiogram (ACG) *O point* occurs with opening of the mitral valve. *RFW* and *SFW* are rapid and low filling waves respectively. See discussion text in regard to measurement of wave percentage amplitude

result in a tracing which was of smaller amplitude distorted a mirror image or otherwise unacceptable The tracing was further observed through several cycles of quiet breathing in order to determine the optimal stage of the respiratory cycle for recording With amplitude as the main criterion this optimum usually occurred at or near full expiration Frequently no tracing at all could be obtained during the inspiratory phase of the cycle, but very rarely a tracing could be obtained during inspiration only In order to minimize extraneous movement the subject was instructed to suspend breathing on a signal from the recorder at the stage of the cycle that he considered to be best for actual recording Precautions were taken to insure that the subject did not perform the Valsalva maneuver

The effects of variation in the pressure with which the cup is applied have been studied systematically in 15 subjects. Pressures of 0.5 1 0 1.5 and 2 pounds were obtained by means of a spring mounted cup. Differences in relative *a* wave size were found to be negligible

Basal recording All subjects were asked not to smoke during the hour preceding a test. Repeated tests on one subject were made at the same time of day and the subject was asked to keep constant the time of the preceding meal Subjects lay at rest for at least 10 minutes before basal recording but it is not claimed that they were in a truly basal state A study test was postponed if there had been precordial pain or if nitroglycerin had been ingested less than 1 hour before the test was due The actual basal record consisted of about ten consecutive complexes

Exercise All subjects exercised on two 9-inch steps. The number of ascents in a 3-minute period was determined from Master's table of the standard double two-step test In order to avoid difficulties with the leads attached for in-exercise ECG monitoring ascent of the two steps was followed by backward descent to the starting point Exercise was stopped prematurely in the event of anginal pain progressive depression of the S-T segment or excessive shortness of breath

Postexercise recording Immediately after exercise the subject resumed the left lateral position. An ACG was not usually obtained in the first minute since it was often impossible to record an acceptable tracing during this period Because postexercise ECGs were also recorded the time after exercise of the first ACG varied it rarely exceeded 3 minutes At least three separate ACG recordings were obtained within 10 minutes of the end of exercise and the precise time of each was noted

Measurement Fig 1 is a typical normal ACG The nomenclature adopted is that recommended by Benchimol and Dimond

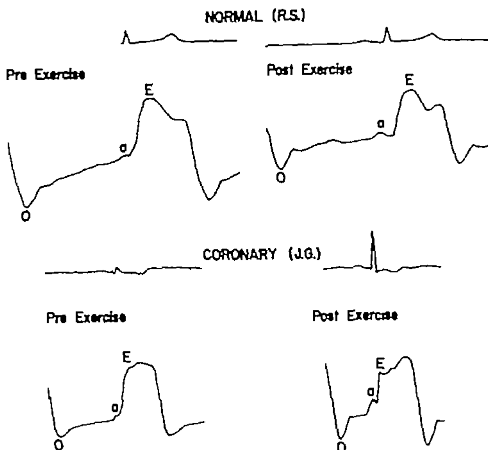


Fig. 2. Typical ACGs before and after exercise in a normal subject and in a patient with CHD. In the normal subject negligible change in aWPA took place but in the patient with CHD there was an increase from 8.1 per cent at rest to 21.6 per cent after exercise. The late systolic portion of the patient's record rose to a height greater than that of the *E* point.

with certain additions.[3-] Attention is confined in this communication to the *a* wave percentage amplitude (aWPA) defined as

$$\frac{a \text{ wave amplitude}}{\text{OE amplitude}} \times 100.$$

By use of these ratios, calibration problems are avoided. The E point, corresponding to the end of isometric contraction, was normally the highest point of the tracing (Fig. 1), but was not necessarily so (Fig. 2). However, in the calculation of the aWPA the O-E amplitude was always used. The *a* wave was in general recognized as a positive deflection, the onset of which was approximately synchronous with the end of the P wave of the ECG. For the purposes of measurement, the onset of the *a* wave was defined as the intersection of the projections of the lines of the slow filling wave and the ascending limb of the *a* wave (Fig. 1). A record reader with micrometer adjustment was available to assist in this definition, but it was necessary to use this only in a minority of the records. More often, satisfactory measurements could be made with a millimeter rule.

In cases in which there was difficulty in precise definition of either the *a* wave or the E point, or both, this could almost always be resolved by the use of time relationships established by Braunwald and associates.[4]

Analysis of data. Standard methods have been used throughout. Reproducibility has been evaluated by analysis of variance. As used in this study, the method yields two quantities, the "within" mean square (WMS) and the "between (or

among mean squares (BMS). The WMS is a measure of variation within the subjects, i.e., from test to test in the same individual. The square root of the WMS is an estimate of the standard error of the variable on successive recordings from a single individual and is thus a measure of *reproducibility*. The BMS is a measure of variation from one subject to another. A BMS which is significantly greater (by the F test) than the corresponding WMS indicates that each individual tends to have a characteristic response which is to some extent reproduced from day to day. When the BMS is consistently large in relation to the WMS, it can be said that reproducibility is not the main factor limiting the usefulness of the variable in question as a discriminator.

Quality of the records. The quality of all of the recordings taken on subjects from Groups A and B was assessed by three of the authors (B.M.B., W.K.H., and R.W.S.). The proportion falling into each class and the criteria of classification were as follows:

GOOD (79 per cent basal, 57 per cent postexercise). A tracing with symmetrical O points, stable base line, and close to the form that we have come to regard as classic.

SATISFACTORY (18 per cent basal, 25 per cent postexercise). A tracing imperfect with respect to symmetry of the O points, stability of base line, or general form. The *a* wave is unequivocally recognizable and measurable.

POOR (1 per cent basal, 14 per cent postexercise). A tracing which fails to satisfy at least one of the above-mentioned criteria, but on which the *a* wave can at least be recognized, even if there is doubt about the accuracy of measurement.

UNSATISFACTORY (2 per cent basal, 4 per cent postexercise). A tracing with little resemblance to classic form or in which the *a* wave cannot be identified with certainty. To avoid bias it was decided before the study began that we should attempt to measure such tracings, but admittedly their measurements are far from true values.

Results

Group data. Table I is a summary of results obtained on the first day of study in the five groups, A, B, C, D, and E. When a subject was studied on more than one day, only the observations on the first day are presented in this table. Although important differences exist between the means

Table I. Summary of data from the five groups (1-day observations)*

	Group A (Normal)	Group B (Coronary heart disease)	Group C (Negative ballistocardiography)	Group D (Positive ballistocardiography)	Group E (Angina pectoris)
Number of subjects	40	41	21	17	16
Mean age (yr.)	47.1	51.8	43.7	41.7	52.4
Basal aWIA					
Mean	8.38	14.26	7.01	12.25	13.59
Standard deviation	3.8	7.6	4.6	6.3	6.1
S.E. of mean	0.60	1.19	1.01	1.31	1.51
Postexercise WIA					
Mean	11.12	25.14	9.09	21.03	20.87
Standard deviation	5.6	11	4.8	9.1	5.4
S.E. of mean	0.89	1.83	1.03	2.21	1.31
Change with exercise					
Mean	[illegible].77	10.91	2.07	[illegible].6	7.[illegible]8
Standard deviation	4	7.0	3.2	5.6	7.7
S.E. of mean	0.75	1.09	0.69	1.[illegible]	1.9

*In this and all following tables, an observation is the mean of three consecutive complexes.

Table II Summary of data from the five groups (3-day observations)

	Group				
	A (Normal)	B (Coronary heart disease)	C (Negative cine arteriography)	D (Positive cine-arteriography)	E (Angina pectoris)
Number of subjects	24	22	9	5	4
Mean age (yr.)	47 1	51 8	43 8	39 2	50 7
Basal WPA					
Mean	7 91	13 65	8 16	10 02	12 42
Standard deviation	3 3	7 1	2 2	4 8	3 9
S E. of mean	0 68	1 52	0 74	2 11	1 94
Postexercise aWPA					
Mean	10 60	22 91	9 74	18 50	17 87
Standard deviation	3 9	9 4	3 6	4 0	4 6
S E. of mean	0 79	2 01	1 21	1 79	2 31
Change with exercise					
Mean	2 69	9 26	1 59	8 48	5 45
Standard deviation	2 1	4 3	2 4	1 6	1 3
S E. of mean	0 43	0 92	0 79	0 71	0 67

of the basal aWPA for diseased and normal groups such differences are much more marked for the means of the postexercise aWPA. The change with exercise namely postexercise aWPA minus basal aWPA is also presented Table II is a comparable summary of 3-day observations for those subjects on whom they were available As would be expected the means do not change significantly but, since by considering the means of multiple observations we are reducing the effective experimental error the standard deviations are in general considerably less than those in Table I

Figs. 3A and 3B are frequency polygons of the basal and postexercise aWPA and the change in aWPA occurring with exercise Data from Groups A B C D and E are included They are presented in pairs in order to give some impression of the discriminating power of the respective variables. The shaded areas represent the overlap for each pair of groups. The 1-day observations in Fig 3A show that the basal aWPA is by itself a poor discriminator with substantial overlap between normal and CHD subjects. The postexercise aWPA is considerably better as evidenced by a much smaller proportion of overlap. The change with exercise although distributed differently appears to have discriminatory power which is similar to the postexercise aWPA. On the right hand side of Fig 3A the improved separation obtained when we deal with 3-day mean observations is demonstrated visually for each variable the amount of overlap is usefully reduced. The distributions in Fig 3B are less reliable since they deal with smaller numbers of subjects. Attention might be drawn however to the relatively good separation shown by the postexercise aWPA with respect to those patients on whom selective cine coronary arteriography was performed For such patients on whom we have objective evidence of coronary artery obstruction the postexercise aWPA appears to be a more useful index of disease than does the change in aWPA.

The differences in means between th normal and diseased groups for the basal postexercise and change in aWPA are all highly significant (by the t test) However we do not emphasize this since such significance per se does not necessarily imply that any or all of its variables are especially effective discriminators. Thus, we are much more interested n the extent of the overlap as an indication of how well or how poorly the method separates normal controls from patients.

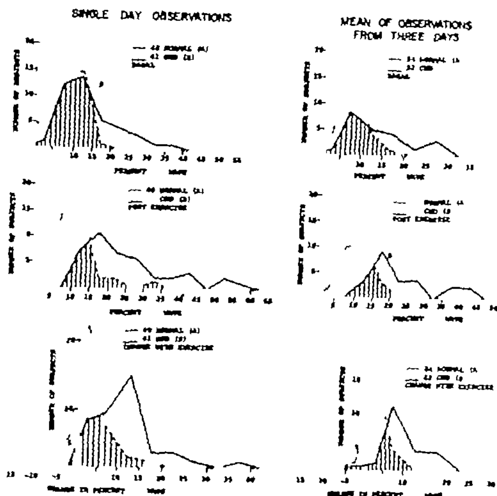


Fig. 3.1 Frequency polygons of aWPA values for normal and CHD subjects with shaded area indicating amount of overlap.

Reproducibility. Analyses of variance relating to the day-to-day reproducibility of the aWPA appear in Tables III, IV, and V. Analysis of the postexercise aWPA was confined to subjects whose records were obtained at comparable times after exercise. For this reason the total in each category is less than the total studied. The mean of each variable is given for normal and diseased subjects. In accordance with convention the coefficient of variation defined as

$$\frac{\text{standard error within subject}}{\text{mean of the group}}$$

has also been calculated; it is a measure of variability relative to the mean. In all three tables, for both normal and diseased subjects, the BMS is significantly larger than the WMS. This implies, as indicated earlier, that reproducibility is not the main limiting factor to the discriminatory ability of the method.

Of the components of variation together determining reproducibility, reader error is the only one which could be effectively isolated. Variation between two readings of one observer (W.M.C.) and between readings of two observers (W.M.G. and B.M.B.) was calculated. Through use of the fact that over-all variance is, assuming independence, the sum of the variances due to each source of variation, reader error is found to account for between 10 and 20 per cent of the total variation. Thus it is not considered to be of great importance.

Effect of time after exercise. Since many

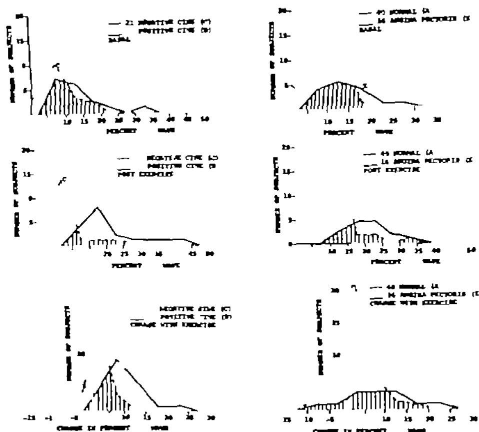


Fig. 3B. Frequency polygons of WPA values for subjects of known cineangiographic status and for subjects with angina pectoris.

of our records were not obtained immediately after exercise, in part because recordings made in the first minute were unsatisfactory. We have tried to explore the likely effect of this delay on our results in comparison with those of other investigators. In only 26 of our 40 first-day Group A records did the maximal aWPA occur in the first readable recording. Similarly in only 28 of our 41 first-day Group B records was the first readable aWPA the maximum. In 15 subjects of Group A who had a readable recording within the first 2 minutes, the average maximum at any time after exercise was 9.4 per cent. In the other 5 subjects of Group A the average maximum aWPA was 12.2 per cent. In the 1 subjects of Group B who had a readable recording within the first 2 minutes, the average maximum aWPA at any time was 25.6 per cent. In the other 20 subjects of Group B the average maximum aWPA was 24.8 per cent. Thus, we do not believe that we missed significant information by failing to obtain records in the first 2 minutes after exercise.

Effect of age. Figs. 4A and 4B show 1-day values (for the first day) of the basal and postexercise aWPA plotted against age on the normal subjects (Group A) and on those with CHD (Group B). The fitted regression slopes provide for each of these two groups an estimate of the expected response of a subject at any given age. The figures also give an impression of the discriminatory value of the aWPA at various ages; thus for the postexercise aWPA there is greater separation

Table III *Reproducibility of basal aWPA*

	Subjects with coronary heart disease		Normal subjects	
Number of subjects	22		24	
Number of test	66		72	
Mean square between subjects	153 10	F = 8.92 p < <.0005	33 33	F = 5 13 p < <.0005
Mean square with subjects	17 17		6 51	
Standard error withi subject	4 14		2 55	
Mean WPA	13 64		7 91	
Coefficient of ariation	0 304		0 322	

Table IV *Reproducibility of postexercise aWPA Analysis of the maximum of three recordings taken within the first 6 minutes after the end of exercise*

	Subjects with coronary heart disease		Normal subjects	
Number of subject	17		16	
Number of tests	42		40	
Mean square between subjects	215 63	F = 5.82 p <.0005	254 6	F = 26.7 p < < 0005
Mean square within subject	37 02		6 358	
Standard error within subject	6 08		2 52	
Mean WPA	22 44		10 83	
Coefficient of ariation	0 271		0 233	

Table V *Reproducibility of postexercise aWPA Analysis of readings matched to within 30 seconds for each subject*

	Subjects with coronary heart disease		Normal subjects	
Number of subject	15		14	
Number of test	45		40	
Mean square between subjects	330 55	F = 8.63 p < <.0005	39 02	F = 2 99 p <.025
Mean square withi subject	38 30		13 05	
Standard error withi subject	6 19		3 61	
Mean WPA	21 73		10 81	
Coefficient of ariation	0 285		0 334	

of the means with advancing age but this is to some extent offset by increasing scatter

Discussion

That the *a* wave of the ACG is directly related to atrial contraction is well established[9] Thus the finding of an increased aWPA in many cases of CHD is more than an empirical observation it is indirect but nonetheless convincing evidence of abnormal atrial activity in these subjects. Consistent with this is the well known occurrence of fourth heart sounds and enlarged atrial components of kinetocardiograms during attacks of angina pectoris [7]

In 1958 Müller and Rørvik[11] observed

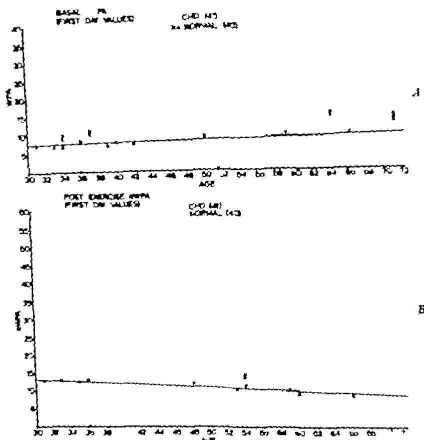


Fig. 4A Regression of basal WPA on age.

Fig. 4B Regression of postexercise WPA on age. Since the variance of the CHD values tends to increase with age regression slopes were fitted through these values by weighted least squares, using the reciprocal of the age as the weight for each case. In normal subjects the variance did not appear to increase with age and lines were fitted by unweighted least squares. Formal significance tests of slope have not been made because the distribution of the errors about the fitted line is clearly not normal.

in a small group of patients that, usually elevation of pulmonary capillary pressure accompanied attacks of angina pectoris induced by light exercise. Since their patients had no evidence of mitral stenosis, they inferred that exercise induced transient left ventricular failure presumably due to ischemia. The work of Braunwald and Frahm[13] showed that left ventricular filling against a heightened left ventricular end-diastolic pressure (LVEDP) could be achieved with relatively slight elevation of mean left atrial pressure (MLAP) or pulmonary capillary pressure by augmentation of atrial contraction. Together these data provide a rational explanation for increased atrial activity during myocardial ischemia; they also suggest the possibility of some quantitative relationship between the aWPA and the height of LVEDP.

There has been little direct observation bearing on the effect of left ventricular ischemia upon LVEDP and in particular the ischemia associated with an attack of angina pectoris. Ross[14] and his associates have repeatedly observed the elevation of LVEDP and anginal pain in patients with CHD undergoing selective coronary cinearteriography. But the issue here is clouded because the injection of contrast medium

alone is apt to cause some elevation of LVEDP even in patients who do not have CHD.[18] Thus the coexistence of high LVEDP with angina pectoris after the injection of contrast medium does not prove a causal relationship. Offsetting this objection are the clear-cut observations of Benchimol and Dimond,[16] Rios and Massumi,[17] and Malmborg[18] that elevation of LVEDP accompanied attacks of angina pectoris when the patients had not received contrast medium. The related studies of Cohen, Gorlin and their associates are at variance with the previously mentioned studies. When they exercised patients with angina pectoris until the induction of pain they found that the rate of left ventricular systolic ejection was regularly decreased but that elevation of LVEDP occurred only if there was simultaneous elevation of systemic blood pressure.

From these conflicting data one can conclude that the myocardial ischemia of angina pectoris may have one of two hemodynamic effects. The potential contribution of apexcardiography to resolving the relative importance of these two effects hinges on the extent to which changes in atrial kick, and hence the aWPA, measure changes in LVEDP. It is unfortunate that neither we nor Benchimol and Dimond investigated systematically the levels of pre-exercise and postexercise blood pressure, as we shall certainly do in the future. The sensitivity of the aWPA to changes in blood pressure is well known and necessitates caution in the use of apexcardiography for investigating myocardial ischemia in patients whose basal systemic blood pressures are elevated.

Although the *a* wave of the ACG and the *a* wave of the ventricular and atrial pressure pulses are surely related, we should not on theoretical grounds alone expect anything *approaching* a precise functional dependence. The left ventricular pressure pulse is a direct measurement of an absolute pressure; the aWPA is an *indirect* measure of a *contributing factor* to such pressure. Highly variable and uncontrollable individual characteristics, such as the position of the heart and the thickness of the chest wall, are necessarily involved in the ACG. Furthermore, the extent to which atrial activity increases in response to elevated LVEDP seems to be likely to vary from one individual to another. Experience so far suggests that the aWPA may be a useful index of change in LVEDP for a given individual, but evidence is lacking to justify its use as an absolute measure of LVEDP.

Since variation from test to test is clearly large enough to interfere with discrimination, we should expect, and do in fact find (Fig. 3), improvement from the use of multiple observations. Further reduction in overlap would be expected if even more observations were taken. However, we know that the variation *among* individuals is large compared with the variation from day to day in any one individual (Tables III, IV, and V); the overlap is thus not mainly attributable to limited reproducibility. If it were possible to determine each patient's true response by an infinite number of observations, a significant degree of overlap would remain. There are two possible explanations for such fundamental overlap: (1) failure to classify correctly the test subjects as diseased or normal before the study, and (2) use of a test criterion which reflects changes neither confined to, nor always present in, CHD. Although we can be reasonably certain that the subjects chosen as having CHD are in fact diseased, we are much less certain that some of our normal subjects do not have latent CHD,[29] and indeed we should expect that some do. If so, the discriminatory power of the test may well be greater than is apparent.

If the discriminatory ability of the aWPA is derived wholly from its relationship with LVEDP, there are then a number of further explanations for the observed overlap. We have already suggested that the aWPA has only a partial correlation with LVEDP and have cited evidence that elevation of LVEDP is by no means a universal accompaniment of CHD, even during attacks of ischemia. Furthermore, elevation of LVEDP is certainly not specific to CHD, and the precautions taken to exclude other known causes of such elevation may have been inadequate.

Benchimol and Dimond[11] reported near perfect discrimination by the aWPA be

tween patients with CHD and control subjects. Their patients had a mean age higher than that of the controls. These authors stated and we have confirmed (Figs. *4A* and *4B*) that the aWPA does not increase with age in normal subjects. Our results indicate however that both the mean and the variance of the aWPA do increase with age in CHD subjects. Although the age difference of the groups studied by Benchimol and Dimond was in a direction favorable to some spurious separation this seems to be unlikely to account for the whole of the disparity between the excellent discrimination which they observed and that presented in Fig. 3. The availability of records from the immediate postexercise period may have been a factor contributing to their better discrimination but our results do not suggest that it was a very important one. It seems to be necessary to suppose that, in comparison to our subjects, their patients were more severely diseased or their controls more certainly free of disease or both.

It is clear from Fig. 3 that the postexercise aWPA is a more effective discriminator than the basal aWPA. This does not necessarily imply that we should reject the basal aWPA it may well be that some combination of the two is more useful than either alone. One simple combination would include the change in aWPA brought about by exercise. This is plausible since as we have already suggested the aWPA appears to be more reliable as an index of change than as an absolute measure of LVEDP. Although it will be seen from Fig. 3 that the change in aWPA does give better discrimination between some of our groups, the improvement could be attributable merely to variation in sampling. An optimal combination for the available data could be found by the technique of discriminant analysis and this approach incorporating also the ECG data will be considered in a separate communication.

It is unfortunate that ACGs of excellent quality cannot regularly be obtained. Before this study began it was decided that every record would be included in the analysis in order to eliminate a possible source of bias. However we consider that approximately 10 per cent of records especially those crucial ones in the postexercise period fall short of acceptable usefulness. Obesity large breasts, pulmonary and pleural disease and inability of the subjects to suspend respiration quietly are contributing limitations to acceptable recording. There are even a few subjects who for a variety of reasons have no detectable apical movement.

Conclusions and summary

The finding by Benchimol and Dimond that the mean *a* wave percentage amplitude (aWPA) is substantially greater in patients with coronary heart disease than in normal subjects especially after exercise is confirmed. The separation with negligible overlap of normal from disease responses found by Benchimol and Dimond did not occur in our study. The likely reasons for this difference are discussed.

The overlap of diseased and normal subjects is partly but not mainly attributable to limited reproducibility either physiological or methodological. For this reason complete separation will not be obtained simply by making multiple observations.

The evidence of some association between left ventricular ischemia and elevated left ventricular end-diastolic pressure (LVEDP) has been reviewed. Reasons for believing that the relative size of the *a* wave of the apexcardiogram may give some indication of this pressure are presented.

We cannot yet recommend the routine use of apexcardiography in the clinical evaluation of patients. We do believe that it has potential application for such use but only after more data have been accumulated relating to its relative diagnostic contribution over and above that of exercise electrocardiography. And finally the use of apexcardiography in the detection of coronary heart disease (CHD) would be on firmer ground if it were demonstrated that transient myocardial ischemia induced by exercise elevated LVEDP independently of the elevation of system blood pressure.

We are indebted to Dr. Edmond A. Murphy and Dr. Richard S. Ross for much helpful advice throughout this study.

Table I. Material

Diagnosis	*Number of cases*
Pulmonary valve stenosis	1
Atrial septal defect	5
Ventricular septal defect	14
Ventricular septal defect and atrial septal defect	1
Ventricular septal defect and patent ductus arteriosus	4
Ventricular septal defect and aortic incompetence	1
Patent ductus arteriosus	2
Aortopulmonary window	1
Tetralogy of Fallot	7
Pulmonary valve stenosis and atrial septal defect	1
Pulmonary infundibular stenosis and atrial septal defect	1
Pulmonary atresia	7
Transposition of great vessels	11
Pulmonary atresia and transposition of great vessels	1
Tricuspid atresia	4
Single ventricle and pulmonary valve stenosis	1
Total anomalous pulmonary venous return	1
Corrected transposition with mitral stenosis	1
Aortic atresia	1
Total	65

which prompted further study by cardiac catheterization, thus accounts for the unusual distribution of cases. Because this was a retrospective study, all of the radiographs reviewed had been taken as a routine investigation. If congestive heart failure had been present at the time of the initial chest radiograph, a later roentgenogram was usually studied. However, for practical purposes, the presence of congestive heart failure did not influence the analysis.

It is the usual practice at this hospital to hold the baby in the erect position whenever possible. The radiograph is taken preferably in the posteroanterior projection but whenever impracticable it is taken in the anteroposterior projection. The tube distance is 5 feet, and the setting used is 55 kv. and 800 Ma., with an exposure time of 0.010 second.

Initially, all of the radiographs were studied by each author independently, and in most cases neither author had prior knowledge of the clinical features or other investigative data. In this way we attempted to be as objective as possible. We then compared our respective observations, and together correlated all of the data.

The factors studied in the chest radiographs were the following: (1) The ratio of the width of the descending branch of the right pulmonary artery to the width of the lower part of the right main bronchus.[8] These structures could be seen easily in the majority of the cases, and their anatomic relationship is demonstrated in Fig. 1. The right descending pulmonary artery was measured at its widest point. For convenience the ratio will be referred to as the A/B index.[9] (2) The ratio of the width of the right descending pulmonary artery to the width of one of its most peripheral branches. This ratio will be referred to as the A/a index. (3) The pattern of the vascularization of the lung, i.e., whether it was lobar and segmental or collateral in type. (4) The relationship between the widths of the pulmonary arteries and accompanying veins.

All 65 infants had been studied by cardiac catheterization. In 11 of these an angiocardiogram had not been considered to be necessary to prove the diagnosis. In 57 cases the anatomic diagnosis had been confirmed by angiocardiography, autopsy, or surgery. A total of 54 angiocardiograms had been recorded and 24 autopsies had been performed. The cardiac catheterization data that were correlated with the chest radiograph in each case consisted, whenever possible, of (a) the ratio of the pulmonary blood flow to the systemic blood flow, which was calculated by comparing the systemic and pulmonary arteriovenous oxygen differences, and (b) the pulmonary arterial pressure. It is recognized that the quantitative calculation of intracardiac shunts on the basis of the blood gas analyses is not entirely reliable, particularly in the presence of very large shunts. However, the data do give a good approximate indication of the relative sizes of the shunts.

Since the pulmonary blood flow itself could not be calculated in the vast majority of these infants, no estimation of the pulmonary vascular resistance could be made. Therefore, for the purpose of this study, we

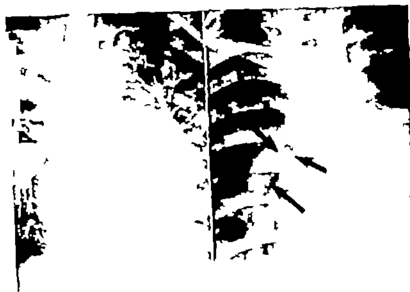


Fig. 3. Bronchogram and plain chest radiograph of same patient illustrating the anatomy of the lower part of the right main bronchus and the descending branch of the right pulmonary artery. In the plain radiograph the upper pair of arrows indicate the bronchus, and the lower pair point to the artery.

have arbitrarily presumed that in those infants with a left-to-right shunt with a pulmonary arterial systolic pressure of 70 mm. Hg or higher some elevation of the pulmonary vascular resistance may be expected. We have also taken a pulmonary arterial systolic pressure of 30 mm. Hg or less to be within normal limits in these infants, and have classified those with a pulmonary arterial systolic pressure of between 30 and 70 mm. Hg as having hyperkinetic pulmonary hypertension.

Results

In only 42 of the 65 cases studied was the definition of the structures under consideration sufficiently clear for objective measurements to be made (Table II). In those cases in which measurements could not be made there was usually a technical radiographic problem such as rotation of the patient or incorrect roentgenographic exposure. In some instances the structures were obscured by a large thymic or cardiac shadow. In the cases in which satisfactory measurements were obtained the following findings were made.

1. The ratio of the width of the descending branch of the right pulmonary artery to that of the accompanying bronchus, the A/B index, was significantly higher in those cases in which there was an increased pulmonary blood flow than in those in which there was a decreased flow (Table II). In those infants with left-to-right shunting the index averaged 3.16, and in only one was it less than 2.0. However, in those infants with a decreased pulmonary blood flow due to right-to-left shunt the average index was 1.11, the highest being 1.6. A glance at Table II will reveal that no quantitative correlation could be determined between the pulmonary to systemic flow ratio and the A/B index. Since several cyanotic infants had an increased pulmonary blood flow, i.e., some infants with transposition of the great vessels or total anomalous pulmonary venous return, these have been classified accordingly in Table II together with the group which had left-to-right shunts.

2. The ratio of the width of the descending branch of the right pulmonary artery to that of its peripheral branch, the A/a index, was of no value in differentiating increased pulmonary flow with normal pulmonary arterial pressure from hyperkinetic pulmonary hypertension or pulmonary hypertension with an increased pulmonary vascular resistance. It should be noted that

Table II Correlation of pulmonary blood flow and pulmonary arterial pressure with A/B index and A/a index

Case number	Diagnosis	Pulmonary: systemic flow ratio	PA pressure (mm Hg)	A/B index	A/a index
A	Increased pulmonary blood flow				
1	A.S.D.	2.0:1	30/3	1.25	3.0
2	A.S.D.	2.5:1	80/48	3.00	2.4
3	A.S.D.	8.0:1	30/1	4.75	6.3
4	A.S.D. Ostium primum	2.5:1	20/5	2.90	5.7
5	A.S.D. and coarctation of aorta	2.0:1	40/12	3.00	
6	V.S.D.	4.0:1	80/45	3.40	3.4
7	V.S.D.	2.7:1	50/20	3.25	6.5
8.	V.S.D.	7.0:1	55/20	2.00	2.0
9	V.S.D.	5.0:1	80/30	2.75	7.3
10	V.S.D.	2.0:1	18/6	3.20	8.0
11	V.S.D.	20.0:1	70/25	2.50	5.0
12	V.S.D.	3.5:1	30/10	4.00	5.3
13	V.S.D.	2.5:1	50/20	4.50	3.0
14	V.S.D.	2.5:1	58/40	2.80	3.0
15	V.S.D.	3.0:1	70/25	4.00	4.0
16.	V.S.D.	20.0:1	60/10	3.00	4.5
17	V.S.D.	3.0:1	95/25	6.60	10.0
18.	V.S.D. and P.D.A.	7.0:1		2.85	
19.	V.S.D. and P.D.A.	5.0:1	90/35	2.60	4.3
20	V.S.D. and P.D.A.	9.5:1	40/10	2.60	4.5
21	V.S.D. and P.D.A.	2.0:1	70/55	4.00	5.3
22.	P.D.A.	4.0:1	33/15	2.85	2.9
23	Aortopulmonary window	15.0:1	45/30	3.60	4.2
24	T.A.P.V.R.	2.5:1	50/12	2.00	2.5
25	T.A.P.V.R. and A.S.D. and V.S.D.	2.0:1	50/6	2.60	6.0
26.	Transposition			3.20	
27	Transposition			3.30	5.0
28	Transposition			2.20	3.25
			Average	3.16	
B	Reduced pulmonary blood flow				
1	P.V.S. and A.S.D.			1.13	
2	P.I.S. and A.S.D.			1.00	
3	Fallot tetralogy	0.90:1		0.83	
4	Fallot tetralogy			1.10	
5	Fallot tetralogy	0.60:1		1.60	
6.	Pulmonary atresia			0.80	
7	Pulmonary atresia			0.60	
8.	Pulmonary atresia			0.83	
9	Pulmonary atresia			1.60	
10	Pulmonary atresia			1.60	
11	Tricuspid atresia	0.25:1		1.00	
12	Tricuspid atresia			1.43	
13	Tricuspid atresia	0.70:1		1.00	
14	Transposition and P.V.S.	0.50:1		1.00	
			Average	1.11	

A.S.D. Atrial septal defect. P.I.S. Pulmonary infundibular stenosis. P.V.S. Pulmonary valve stenosis. P.D.A. [illegible]. T.A.P.V.R. Total anomalous pulmonary venous return. V.S.D. Ventricular septal defect.

in this series, however even those infants with a pulmonary arterial pressure at or near systemic level had a considerable increase in pulmonary blood flow The pulmonary vascular resistance in these cases would therefore be only slightly elevated and none of the cases studied could be deemed to fall into the category of the Eisenmenger syndrome

Pulmonary arterial pressures in the group with a decreased pulmonary blood flow are not reported in Table II chiefly because in the vast majority of these infants the catheter did not enter the pulmonary artery but also because differentiation between increased pressure and increased flow is not a consideration in this group.

3 A lobar and segmental distribution of the pulmonary arteries was noted in all but one case. This observation corresponded with the anatomic verification in those cases in which angiocardiography autopsy or surgery had been performed In most of the infants with pulmonary atresia a large patent ductus arteriosus was shown to provide the pulmonary blood supply In the only infant with a collateral pattern of vascularization autopsy had confirmed the presence of pulmonary atresia and a collateral circulation formed by dilated bronchial arteries (Fig 2)

4 In almost all of the radiographs studied it was not possible to find comparable veins and arteries. In those few cases which did prove to be suitable, comparison of the width of the pulmonary arteries and veins

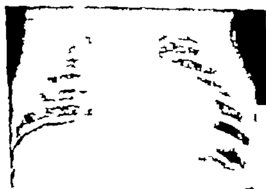


Fig 2. Plain chest radiograph of infant with pulmonary atresia illustrating bronchial collateral vascularization of the lungs.

failed to distinguish between pulmonary hypertension and an increased pulmonary blood flow In one case of corrected transposition of the great vessels and an anomalous attachment of the mitral valve producing mitral stenosis, the veins were observed to be wider than the arteries this observation had in fact been made prior to the cardiac catheterization angiocardiography and autopsy

Discussion

Several workers have observed a correlation between the roentgenographic appearance of the pulmonary vessels and the presence of pulmonary hypertension [1] Essentially these observations have been subjective but they have been made by very experienced observers. Their objective confirmation may be found in Abrams measurements of the descending branch of the right pulmonary artery and its peripheral branch [2] In his study of a small number of adults, he also drew a correlation between the sizes of these vessels and pulmonary blood flow The application of his criteria to the study of the pulmonary vasculature in infants and children is obviously impeded by the varying sizes of the pulmonary vessels in different age groups Measurements of the normal right pulmonary artery in adults have been established [3] However no such normal values are available in infants and children.

To overcome the expected discrepancy in the sizes of the pulmonary vessels in different age groups, we have attempted to standardize measurements by comparing two structures which would have the same expected rate of growth namely the descending branch of the right pulmonary artery and the lower part of the right main bronchus Ros[i]ski first observed that the lumina of the artery and associated bronchus were equal This concept was amplified by Wojtowicz,[4] who used tomography to compare the widths of the arteries and their associated bronchi at several levels in different age groups, and termed this relationship the a/b index " The measurements from which our A/B index is derived correspond with Wojtowicz lower index of the right pulmonary artery " which he found to be 1 28 ± 0.48 i [illegible] year age group His statistics

cate that values of the a/b index are independent of age and sex but no normal values have been determined in infants.

Subsequent observations by one of us (L.S.) support these statistics. Measurements of the A/B index in plain roentgenograms in a group of 43 normal adults averaged 1.14 and in a group of 21 normal infants and children under 14 years they averaged 1.20. These figures fall well below the average A/B index of 3.16 which we demonstrated in the infants with increased pulmonary blood flow.

A further observation that emerged from our study was that the A/B index did not alter over a period of 6 to 12 months in those few cases in which serial roentgenograms were available. In one patient cardiac catheterization at the age of 5 months revealed a ventricular septal defect with an enormous left-to-right shunt confirmed by angiocardiography (Case 16 in Table II). When this infant was 1 year old there was clinical evidence that spontaneous closure of the defect had occurred and this was confirmed on the basis of blood gas analyses during right heart catheterization. Further evidence for the possibility of a small left-to-right shunt was not sought. The pulmonary arterial pressure had fallen to 28/5 mm. Hg. The A/B index at that time remained unchanged at 3.0 and the next available roentgenogram when the child was 3 years old showed an A/B index of 1.75.

Although a high ratio of the width of the descending branch of the right pulmonary artery to the width of its peripheral branch (the A/a index) is a feature of pulmonary hypertension in adults,[2] no such correlation was determined in this group of infants. It is pointed out, however, that in this series no cases were studied in which the pulmonary vascular resistance was proved to be significantly elevated; elevation is surmised on the basis of pulmonary arterial pressures near systemic levels.

Furthermore, in our study technical difficulties in interpretation made it impossible to compare the widths of the arteries with their corresponding veins. We were unable therefore to determine the applicability to infants of Abrams' observations[3] in adults that the pulmonary veins are dilated in the presence of an increased pulmonary blood flow but are smaller than their corresponding arteries if the pulmonary vascular resistance is elevated. It is thought that tomography would be necessary for adequate studies of this nature.

It is difficult to know whether a significant variation in the size of the pulmonary arteries occurs during the phases of respiration. Westermark[1] observed that on inspiration, when the intra-alveolar pressure decreases, the filling of the pulmonary artery increases with consequent enlargement of the vessel and that on expiration the reverse is true. Chang[1] confirmed these observations. However, Abrams[3] pointed out that only slight alterations in measurements were produced by an increase in the intrathoracic pressure, unless this was sustained for a significantly longer period than is employed during routine chest roentgenography, i.e., for 15 to 20 seconds or longer. If it is possible to apply the latter observations to infants, one would trust that, even during periods of prolonged crying, the alteration in pulmonary arterial size would not be great.

The A/B index may alter by 0.1 because of a changing size of the vessels with pulsations, particularly if an exposure time of 0.01 second is used.[2] This is a negligible change which in no way disturbs our results.

This study is limited by having few normal subjects for comparison. However, it is thought that the differentiation between the two large groups of "pulmonary plethora" and "pulmonary oligemia" becomes reasonably clear cut. It is probable that if careful attention is paid to radiographic technique a higher proportion of cases may become amenable to study than we found possible in our small series. The age group that we selected for study is probably more difficult than any other; this has been confirmed by our preliminary observations in a number of older infants and children in whom structures were more clearly defined and measurements were more easily made, and in whom the same criteria appeared to be valid.

Summary

This study has demonstrated that a reliable guide in the gross roentgenographic assessment of the pulmonary blood flow in infants with congenital heart disease is pro-

vided by comparing the width of the descending branch of the right pulmonary artery with that of the lower part of the right main bronchus. This ratio was significantly higher in those infants with an increased flow than in those with oligemic lungs.

The radiographic criteria on which a diagnosis of pulmonary hypertension is made in adults did not apply in infants. Indeed, no reliable evidence of pulmonary hypertension could be obtained in this age group on radiographic grounds. No suitable assessment of the pulmonary venous system could be made in these cases with the radiographic technique that was used.

We are very grateful for the advice and criticism of Dr L. G. Davies, who was in charge of all of the patients studied.

REFERENCES

1. Chang, C. H. The normal roentgenographic measurement of the right descending pulmonary artery in 1,085 cases, Am. J. Roentgenol. 87:929, 1962.
2. Abrams, H. L. Radiologic aspects of increased pulmonary artery pressure and flow. Preliminary observations, Stanford M. Bull. 14:97, 1956.
3. Goodwin, J. F., Steiner, R. E., and Lowe, K. G. Pulmonary arteries in mitral stenosis demonstrated by angiocardiography, J. Fac. Radiologists 4:21, 1952.
4. Davies, L. G., Goodwin, J. F., Steiner, R. E., and van Leuven, B. D. Clinical and radiological assessment of pulmonary arterial pressure in mitral stenosis, Brit. Heart J. 15:393, 1953.
5. Schwedel, J. B., Escher, D. W., Aaron, R. S., and Young, D. The roentgenologic diagnosis of pulmonary hypertension in mitral stenosis, Am. Heart J. 53:163, 1957.
6. Johnson, P. M., Wood, E. H., Pasternack, B. S., and Jones, M. A. Roentgen evaluation of pulmonary arterial pressure in mitral stenosis, Radiology 76:541, 1961.
7. Steiner, R. E. Radiology of pulmonary circulation, Am. J. Roentgenol. 91:249, 1964.
8. Brock, R. C. The anatomy of the bronchial tree, ed. 2, London, 1954, Oxford University Press, p. 11.
9. Wójtowicz, J. Some tomographic criteria for an evaluation of the pulmonary circulation, Acta Radiol. Diagnosis 2:215, 1964.
10. Rowinski, K. Quoted by Wójtowicz.
11. Westermark, N. Importance of intra-alveolar pressure in diagnosis of pulmonary diseases, Radiology 50:610, 1948.

Experimental and laboratory reports

Primary tumor of the glomus pulmonale producing pulmonary stenosis in a Boston terrier

*Brunildo A Herrero Capt M C**
Allen E Ecklund Capt V C
U S Army Edgewood Arsenal Md

This case report deals with a disease process of mutual interest and importance to human and veterinary physicians

The glomus pulmonale was first described as a distinct entity by Krahl in 1960 He defined it as a mass of true glomus tissue found in the adventitia on the dorsal aspect of the bifurcation of the pulmonary artery This body varies in size and configuration with different species. Man has a well-circumscribed single mass of glomus tissue whereas dogs have 5 6 separate masses of glomus tissue covering an area of 2 3 mm The blood supply is from the pulmonary artery and the nervous innervation from the vagus nerve. It has been studied in the rat, cat, dog cow small monkeys, bats chimpanzee and in the human subject.[1-4] It is suspected that this glomus may be functionally related to other glomera (aortic carotid) as a chemoreceptor

Although tumors of other glomera have been described in many species including man a search of the veterinary and medical literature revealed no case reports of tumor of the glomus pulmonale. This report describes the first known instance of a tumor of the glomus pulmonale It also presents this tumor as another potential cause of acquired pulmonary stenosis

Case report

This 11-year-old female Boston terrior was brought by her owner to the Post Veterinary Clinic December 1962 with abdominal swelling for period of time consistent with gestation She had been seen intermittently since 1957 for recurrent otitis externa and no cardiovascular abnormalities had been noted Pertinent physical findings consisted of marked ascites and a heart murmur which was not described further Examination of the peripheral blood for microfilaria of *Dirofilaria immitis* was negative. Abdominal roentgenograms were conclusively negative for pregnancy Treatment with digitalis and chlorothiazide produced improvement. However on Feb 15 1963 the animal again presented with increasing ascites and peripheral edema involving the rear limbs The same treatment was intensified but the response was poor On Feb. 25 1963 the dog was euthanized at the owner request.

Physical examination prior to euthanasia revealed marked abdominal swelling with severe ascites, 4+ pitting edema of the hind limbs, and jugular distention. Palpation of the chest revealed large forceful parasternal heave and a thrill over the pulmonary area A Grade 6/6 harsh murmur was heard over the pulmonic area with radiation into both axillae and dorsally to the interscapular area. The murmur was present throughout systole and part of diastole. The quality of A and P was not discerned because of the intensity of the murmur The lungs were clear to percussion and auscultation, and there was no evidence of pleural or

From the Experimental Pathology Section, Directorate of Medical Research, Chemical Research and Development Laboratory United States Army Edgewood Arsenal, Md.
Received for publication March 1, 1966.
Present address Department of Medicine Duke University Medical Center Durham, N. C., 27706.
**Present address: Braham, Minnesota.

pericardial effusion. Roentgenograms of the chest revealed clear lung fields, cardiomegaly and a round opacity in the area of the pulmonary artery near the bifurcation of the trachea. Films of the abdomen revealed the typical ground-glass appearance of ascites. A hemogram was normal.

A complete postmortem examination followed euthanasia, with the findings as follows: The abdominal cavity contained 2 liters of reddish-tinged fluid with a hematocrit of 1 per cent. No excess fluid was present in the pleural or pericardial cavities. The liver was enlarged and appeared to be markedly congested, with a prominent centrolobular pattern. The heart was enlarged and weighed 130 grams (normal, 80 grams). There was marked right ventricular hypertrophy and dilatation. The myocardium was flabby and measured 0.5 cm. on the right side and 1.2 cm. on the left. The tricuspid valve was somewhat dilated, measuring 8.5 cm. at the valve rings, and appeared to be slightly insufficient. The other valves were essentially unremarkable. Just above the pulmonary valve a 0.5- by 1.3-mm., yellowish, firm atherosclerotic plaque was present in the intima of the pulmonary artery.

A well-circumscribed oval to slightly irregular tumor was imbedded in the mediastinum between the dorsal portion of the pulmonary artery near the bifurcation and the trachea. It measured 2.2 cm. in greatest diameter and was rather firm in consistency and of light tannish brown to yellow in color. There was slight dimpling centrally. Before the connective tissues of the mediastinum were dissected away from the tumor it was clearly evident that the main branches of the pulmonary artery were displaced, stretched, and considerably narrowed by the mass. The dorsal aspect of the tumor was well encapsulated and easily detached from the surrounding structures. Ventrally the tumor was intimately attached to the outer layer of the pulmonary artery wall just above the bifurcation and to the left pulmonary artery branch. Figs. 1 and 2 show the location of the tumor and the distance away from the aorta and the ductus arteriosus which remained as a fibrous, sealed structure. Dissection of the mediastinal connective tissue around the tumor resulted in correction of the pulmonary stenosis.

Histologically the tumor was typical of and identical to tumors of the carotid body and aortic body. Fig. 3 shows a very low-power view to demonstrate the relationship of the tumor to the adventitia of the pulmonary artery at the bifurcation. Normal glomus elements and a transition zone are clearly shown in Fig. 4. The detailed morphology is demonstrated at high magnification in Fig. 5. An alveolar pattern with its reticular stroma and vacuolar elements is well seen. Local invasion or metastases were not present. Bioassays were not performed on the tumor.

Discussion

Neoplasms of the "chemoreceptor system" are found in both human beings and animals. The greatest difference between the species is the relative frequency of involvement of the various components of



Fig. 1. The tumor (T) as it appeared after the mediastinal connective tissue was dissected away and the pulmonary artery branches were decompressed. The aorta (A) is pulled ventrally by a hook to demonstrate the ligamentum arteriosum (LA).

the "chemoreceptor system." Anatomically specific and histologically similar bodies of glomera have been isolated and identified in various locations. The carotid body was first described by Von Haller in 1743. Similar cells were described in the ciliary body of the chimpanzee by Botar and Pribek in 1935. The jugular body was described by Valentin in 1840 and rediscovered by Guild in 1941. The aortic-pulmonary complex was first described by Bieal and Wiesel in 190_. Since that time it has been shown that this group of bodies is made up of a paraganglion related to the ductus arteriosus, one located anterior to the pulmonary artery near the origin of the left coronary artery, one near the innominate artery, and another group on the anterior aspect of the aortic arch (supra-aortic bodies). The inferior aortico-



Fig. 2. Note the relationship of the tumor (*T*) to the dorsal aspect of the pulmonary artery at the bifurcation. The aorta (A) and ligamentum arteriosus (*LA*) are free of involvement.

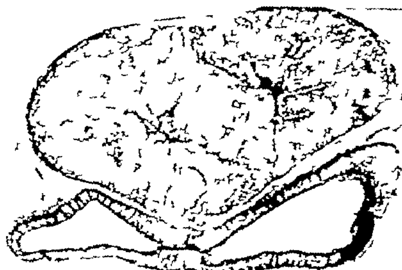


Fig. 3. This shows the relationship of the tumor to the dorsal aspect of the pulmonary artery at the bifurcation.

pulmonary glomus described by Boyd was once named the ***glomus pulmonalis*** by Nonidez. The blood supply to this glomus is from the pulmonary artery only in early life. The glomus pulmonale described by Krahl is clearly located on the dorsal aspect of the pulmonary artery and is supplied by this artery in adult life.

Tumors of the carotid body are relatively frequent in human beings, and over 350 cases have been reported. Many excellent reports are available. Tumors histologically similar to tumors of the carotid body have been described in the mandible, retroperitoneum, and thigh by Byrne.[1] Tumors of the aortic body are very rare in human beings but have been reported by Lattes,[1] MacDonald,[11] and Duncan. In contrast, tumors of the aortic body are relatively common in dogs, and tumors of the carotid body are very rare. Tumors of the carotid body



Fig. 4. This photomicrograph is of the transition zone with pulmonary artery wall above (*1*), normal glomus elements in the mid-portion (*2*), and tumor below (*3*).

have been reported by Jubb and Kennedy,[14] Scotti,[15] and Hubben, Patterson and Detweiler.[1] Since the report on the structure and histogenesis of tumors of the aortic bodies in dogs by Bloom[17] in 1943, many cases have been studied and reported. Mulligan coined the term *chemodectoma* in 1950 to apply to neoplasms consisting of chemoreceptor cells which are associated with the distribution of parasympathetic nerves and which originate either in the adventitia of blood vessels in structures intimately connected with afferent nerve fibers, or which occur along the branches or in the ganglia of the glossopharyngeal and vagus nerves. We are reluctant to call our tumor a chemodectoma because the chemoreceptor function of the glomus pulmonal has not been established.

For many years, veterinarians have been aware of the syndrome referred to as the "heart base tumor." These neoplasms have been observed in the cow, horse, sheep, dog, and fowl. Of 80 cases of heart base tumors collected by 1958, 20 arose from free thyroid tissue, 5 from parathyroid origin, and 55 from the aortic body. Nilsson's report,[20] in 1955, dealt with 40 cases, and the present series at



Fig. 5. This high-powered photomicrograph of the tumor reveals the typical carotid-body like appearance with clumps of cells in [illegible] pattern and surrounding reticular elements. Vascular elements are prominent.

the University of Pennsylvania School of Veterinary Medicine consists of over 60 cases of heart base tumors within canine species.[22] One of these cases was thoroughly discussed in a reported clinical pathologic conference.[23] These tumors almost always are found between the aorta and pulmonary arteries. They can reach huge proportions and sometimes wrap around the great vessels. There is frequent involvement of the pericardium which results in significant effusions. Hemodynamically there is restriction of inflow into the heart and pericardiocentesis alleviates many of the signs. Edema is usually most severe in the head, neck, and forelimbs. Ascites is common. The hind limbs are frequently associated with the above-mentioned signs. Murmurs are usually not present. Most of the reported cases would be considered to be unresectable lesions. There is an overwhelming and unexplained incidence in brachiocephalic dogs (boxers, bull dogs, Boston terriers) as compared to other breeds. Pedini[24] reported an excellent example of this condition in a pointer. Because of their large size and diffuse involvement it is frequently impossible to determine precisely the origins of many of these tumors.

The tumor presented in this case report can be placed in the broad category of a heart base tumor However it differs in its clinical manifestation from the usual heart base tumor in that its major features are those of obstruction to outflow from the right ventricle with right-sided heart failure rather than obstruction to inflow into the right side of the heart from the anterior part of the body Paterson[21] LeCompte[24] and Krahl have not seen or heard of a case similar to this one.

The human medical literature contains relatively few reports of acquired pulmonary stenosis. The underlying disease processes reported have consisted of advanced miliary tuberculosis[25] rheumatic valvular disease[26-29] rheumatic pericarditis,[30] bacterial endocarditis,[31-34] atherosclerosis,[35] aortic aneurysm[36] primary tumor of the pulmonary valve,[37,38] malignant carcinoid[39-41] pericardial band[42] thymic neoplasm[43] teratomas,[44-46] lymphoma[47] and fibrosarcoma of the pulmonary artery Now that existence of tumor of the glomus pulmonale has been documented in one species it is reasonable to assume that it occurs in man and that it will eventually be found It is also reasonable to assume that it may manifest itself as another cause of acquired pulmonary stenosis.

Summary

To our knowledge this case represents the first instance of a primary tumor of the glomus pulmonale. It is also the first instance of this type of tumor producing acquired pulmonary stenosis. Tumors of the chemoreceptor system occur in human beings as well as in the canine species thus, this entity is a potential source of acquired pulmonary stenosis in human beings which might be surgically curable. We hesitate to call this tumor a chemodectoma since the function of the glomus pulmonale has not been firmly established

We wish to thank Mr Raymond E. Lund of The Johns Hopkins Hospital Department of Pathology for the photographic assistance.

REFERENCES

1 Krahl, V E.: The glomus pulmonale (preliminary report) Bull. School Med Univ Maryland 45:36, 1960.
2. Krahl, V E. The glomus pulmonale Its location and microscopic anatomy Ciba Foundation Symposium on Pulmonary Structure and Function, 1962 p. 53.
3 Krahl, V E. Personal communication.
4 Barnard, W G.: A paraganglion related to the ductus arteriosus, J Path. & Bact. 58:631 1946
5 Boyd, J D The inferior aortico-pulmonary glomus, Brit. M Bull. 17 127 1961
6 Nonidez, J F Observations on the blood supply and the innervation of the aortic paraganglion of the cat, J Anat. 70:215 1936.
7 Gratiot, J H Carotid body tumors (collective review) Internat. Abstr Surg 77:177 1943
8. Donald, R. A and Crile, G J Tumors of the carotid body Am J Surg 75:435 1948.
9 LeCompte, P M Tumors of the carotid body and related structures (chemoreceptor system) In Atlas of tumor pathology (Section 4-Fascicle 16) Washington, D C., 1951 Armed Forces Institute of Pathology
10. Byrne, J J Carotid body and allied tumors, Am. J Surg 95:371 1958.
11 Lattes, R. Nonchromaffin paraganglioma of ganglion nodosum, carotid body and aortic arch bodies, Cancer 3:667 1950.
12. MacDonald, R. A. A carotid body like tumor on the left subclavian artery Arch. Path 62 107 1956.
13 Ducan, D K. and McDonald J R Chemodectoma (nonchromaffin paraganglioma) of the mediastinum. Report of two cases, Am. J Clin Path. 21:515 1951
14. Jubb, K. V and Kennedy P C. Tumors of the nonchromaffin paraganglia in dogs, Cancer 10:89 1957
15 Scotti, T M. The carotid body tumors in dogs, J Am. Vet. M.A. 132:413, 1958.
16. Hubben, K., Patterson, D F and Detweiler D K. Carotid body tumors in dog J Am. Vet. M.A 137:411 1960.
17 Bloom, F Structure and histogenesis of tumors of the aortic body in dogs, Arch P th. 36 1 1943.
18 Mulligan, R H. Chemodectoma in the dog, Am. J Path 26:680, 1950
19 Dobberstin, J P llaske, G and Stunzl, H editors Handbuch der speziellen pathologischen Anatomie der Lanstiere ed 3 2 71 1962 (translation by Joyce R Bradley C C.S.U U iv of Pennsylvania Vet School, Philadelphia, Pa.)
20. Nilsson, T Heart base tumor in the dog, Acta Path. Scandinav 37:385 1955
21. Paterson, D F Personal communication
22. Brodey R. S., and Prier J E. Clinical pathological conference from the School of Veterinary Medicine University of Pennsylvania, J Am V t. M.A. 141 739 1962
23. Pedini, B. Tumors della base del cuore nel cane, Estratto da Veterinaria Italiana R Vista di Igiene, Profilassi Terapia, pp 1 16, 1957
24 LeCompte, P M Personal communication
25. Gilmore, H. R J Tuberculosis involving the pulmonary valve Am. J P th 16:229 1940
26. Herbiet, J U cas de stenose pulmonaire

acquisé d ongenil heumatismale Bruxelles Med 36 1425 1956 Quoted by Babcock [a]

27. McCune J nd M Sama R J Orig n nd lative insufficiency of the pulm nary v l Am H art J 14:562 1937
28. Schwartz S I nd Shelling, D Acq ired rheumatic pulmonic tenosis and insufficienc Am Heart J 6:568 1931
29. Griffith G C Report of ase of heumatic heart disease, th invol ement of both mitral nd p lm onic valves M Clin North America 18:233 1934
30. Goules B A Constriction of the p lmonary artery by adhesiv pericard tis, Am Heart J 13 470 1937
31. Brandes, W W T ses of malignant ulcer th endocardit of the pulmonary l e, Chicago P th Soc T 13:217 1935 Quoted by Babc ck [a]
32. Billings, F Chronic infect us endocarditis, Ar h Int Med 4 409 1909
33. Gr yael D M Pulmonic endocardit A clinical nd pathologic l report of three cases Y le J Biol & Med 7:515 1935 Quoted by Babcock [a]
34. Whipman T R A heart showing unf t pol poid thrombus in the pulmonary artery and extend ng into the ight entricle and mistaken f r patent ductus arteriosus Pr c Roy Soc Med (Children section) 4 199 1911 Quoted by Babc ck [a]
35. Donager C R Sten sis of the pulmonary due severe theroma, J P th & Bact 48:472 1939
36. Bufah s, F Duplice simmetrico aneurisma della porzione scendente dell arc aortico on esito in steno dell arteria polmonare pseud tuber ulos polmonare Riv di Clin Med 28:350, 1927 Quoted by Babc ck [a]
37. Richmond R nd Price, H P Papillary fibr oma of the pulmonic alve Report of se J M Soc New Jersey 32:353 1935 Quoted by Babcock [a]
38. Dean, C nd F lconer A. W Primary tumor of the v lves of the heart J P th & Bact 18:64 1913
39. Millman, S Tricuspid tenosis and pulmonary tenosis omplicating carcinoid of the intestine with meta tases t the liver Am Heart J 25:391 1943
40. Jenkins, J S nd Butcher F J A M lignant argentaffinoma th cy nosis and pulmonary t nosis, Lancet 1 331 1955
41. R berts, W C and Sjoerdsma A The cardiac disease sociated th the carcinoid yndrome (carcinoid heart disease) Am J Med 36:5 1964
42. McGaff C J Haller J A, Leight I and T wers B T Subvalvular pulmonary te nosis due to onst iction of the right entricular outflow tract by pericardial band, Am J Med 34 142, 1963
43. Winter B Pulmonic enosis produced by compression of heart by terior mediastinal tumor Am H rt J 18, 1958
44. Fry W Klein C I nd Barton H C Malignant mediastinal teratoma imulating cardiovascular disease Dis Chest 27:537 1955
45. Rusby N L Dermoid cy ts nd teratoma of the mediastinum A review J Thoracic Surg 13 169 1944
46. M er H C Dermoid cy ts nd teratomas of the mediastin m ith unusual features, Arch Surg 57 154 1948
47. Babcock, K B Judge, R D nd Rook tein J J Acquired pulmonic tenosis Report of case caused b media tinal neoplasm Circ la tion 26:931 1962
48. W ll F E Dickenma R C nd Langst n, J D Fibr sarcoma of the pulmonary artery masquerading pheochromocyt ma, Am J Clin P th 34 146, 1960

Histogenesis of experimentally induced myositis ossificans in the heart

Hans Selye M.D. Ph.D.
Shakuntla Mahajan M.D.
Raghbir Singh Mahajan M.D.
Montreal, Canada

Earlier experiments have shown that the subcutaneous implantation of certain "tissue scaffoldings," e.g. glass rings, frequently results in ectopic ossification within the connective tissue delimited by these objects. This type of bone formation was almost constantly associated with the development of hemopoietic tissue and of irregularly distributed cartilage plates in which endochondral ossification was in progress. Here ossification was induced by a chemically inert foreign body of a given shape presumably because of purely mechanical reasons. However, by this means osteogenesis could not be obtained consistently; the incidence varied greatly from one experiment to another and hence the procedure, although demonstrating the possibility of mechanical induction of bone, did not lend itself well to use as a standard model.

More recently, we have been able to develop a surgical technique for the reproducible induction of bone formation in the heart of the rat. This procedure, described as the "ventricular ligature," consists of the complete occlusion of the cardiac apex by a strongly constricting ligature placed around both ventricles at the level of the border line between their middle and lower thirds. The portion of the cardiac muscle that lies below the ligature undergoes necrosis and is replaced by a membrane of cicatricial tissue in which bone, bone marrow, and cartilage are regularly formed.

It was tempting to assume that in both the tissue scaffolding and the cardiac ligature techniques the osteogenic stimulus is a mechanical one. Although this has not yet been definitely demonstrated, the latter procedure provides us with a reliable model for the production of bone without the use of any chemical osteogenic inductor substance. It is the object of this communication to report on the histogenesis of this form of ectopic ossification.

Materials and methods

In 20 Sprague-Dawley rats with an initial average body weight of 100 grams (range from 90 to 110 grams), the lower third of both ventricles was tied off by a constricting ligature without the use of pressure respiration, as follows.

The fur is removed from the chest region with electric clippers. Then the animal is

From the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Quebec, Canada.
This work has been supported by the John A. Hartford Foundation and the Medical Research Council of Canada.
Received for publication April 11, 1964.
Address: Institute of Experimental Medicine and Surgery, University of Montreal, C. P. Box [illegible], Montreal, Que., Canada.

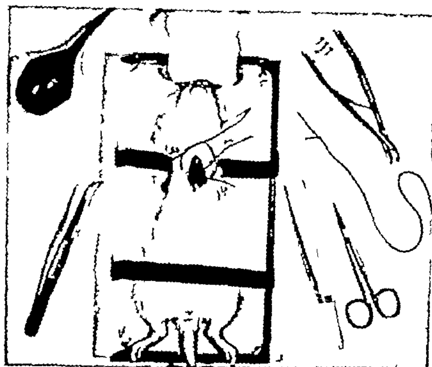


Fig. 1. Operating table as it appears just after the ventricular ligature is tied. The fur is clipped in the chest region and the animal is tied to the operating board by rubber bands. A gauze pad for the application of ether is near the snout. To stabilize the head the incisor teeth are hooked into a metal loop that is fastened to the table. Note: rubber syringe, blunt curved forceps, Michel clips and clip forceps, needle with black thread (for cutaneomuscular stitch), small pointed scissors, and second curved forceps. Ligatures are also shown in position.

placed under a bell jar and lightly anesthetized with ether. After this, it is fastened to an operating board: two strong rubber bands immobilize the legs and pelvis whereas, to hold the head steady, the upper incisors are hooked through a wire loop fastened to the board itself (Fig. 1). During preparation for thoracotomy additional anesthesia may be administered if required by placing an ether-soaked gauze pad over the head but no more anesthetic is given once the thorax is opened.

It is unnecessary to observe strictly aseptic precautions but we always cleanse the skin with an antiseptic (Metaphen) prior to surgery, use sterile instruments and towels, dip the instruments into Metaphen after every two or three operations and treat the animals with an antibiotic (Terramycin) during the 5 days after the intervention. As a result of these precautions, infections are quite exceptional.

The small operating board is placed on a table with the rat's tail toward the surgeon who wears a binocular loupe and a strong frontal lamp to improve vision. A craniocaudal incision of about 2 cm. is made parallel with and slightly to the left of the sternum through the skin and pectoral muscles to expose the ribs. Thereupon a straight needle is inserted near the middle of the lateral margin of the wound and carried through a tunnel of pectoral muscle tissue around the cranial half of the incision to emerge again on the lip of the wound at a point facing that through which the thread was introduced. The ends of this cutaneomuscular ligature are loosely knotted and laid on the neck of the animal out of the surgeon's way so that the thoracotomy wound may be closed immediately after the operation by merely tightening the knot.

A blunt curved forceps is then plunged between the fifth and sixth ribs, through the intercostal muscles at a point approximately 2 mm. to the left of the sternum

Thereby bleeding from the internal epi gastric artery (which courses just to the left of the sternum) can be avoided The gap is then widened to about 15 mm. by gentle lateral pressure with the perforating forceps, while the sixth rib is held steady with another curved forceps. At this time the rapidly beating heart becomes visible. Air now enters the chest cavity and respira tion becomes impossible but this does not matter since the intrathoracic part of the operation takes only 60 to 90 seconds.

The sixth costal cartilage is transected with fine pointed scissors about 0.5 cm. to the left of the sternum one forceps holds the sternal end of this cut rib in position whereas the other enters the thorax to sever the pericardium and ex teriorize the heart. Light pressure upon the thorax helps bring the heart to the outside without damage. Then a thick (noncutting) ligature is placed around the whole heart, encompassing both ven-tricles at the junction line between the middle and lower thirds. This ligature is tied as tightly as possible without cutting into the musculature (Fig 2)

The heart is now replaced into the tho-rax, and the previously placed cutaneo-muscular thread is tightened to close the thoracic wall. Slight lateral pressure im mediately after this ligature has been tied squeezes the air out of the thorax and since the skin subcutaneous tissue and muscles act as a valve breathing immedi-ately becomes possible again Should res-piration be slow to start or be impeded by the accumulation of mucus a rubber syringe is introduced into the throat to remove any blockage The operation is then terminated by placing one Michel clip above and one below the cutaneo-muscular stitch to assure perfect closure of the thoracic cavity The intervention takes approximately 2 to 3 minutes from skin incision to completion of wound clos-ure (All necessary instruments are shown in Fig 1)

Ten of the rats were put to death with chloroform after 30 days, and the remain ing 10 after 60 days The hearts were fixed in Susa solution saturated with picric acid for subsequent staining with the PAS and multipurpose polychrome tech niques[3] the latter being especially appropri ate for the demonstration of elastic fibers and smooth muscle tissue



Fig 2 Central part of Fig 1 at higher magnification. Note cutaneomuscular ( ) and ventricular (b) ligature.

Results

At autopsy the hearts were found to be greatly enlarged in both the 30-day and the 60-day group. The portion below the ligature was thin but dilated and some times filled with mural thrombi whereas the part above the ligature underwent intense compensatory hypertrophy In all instances adhesions connected the heart to the anterior wall of the thorax and to the lungs. The thread of the ligature either slipped toward the apex or cut through the entire thickness of the ventricles be-cause it became too tight as the hyper trophy and dilatation gradually increased In the latter case part of the circumference of the ligature came to lie within the car diac cavity usually enveloped in throm botic material

After the heart was opened and clots and mural thrombi were flushed out, the endo-cardium was seen to be thickened. How ever whereas the rats killed after 30 days showed no other macroscopically visible change those allowed to survive for 60 days exhibited hard cartilaginous

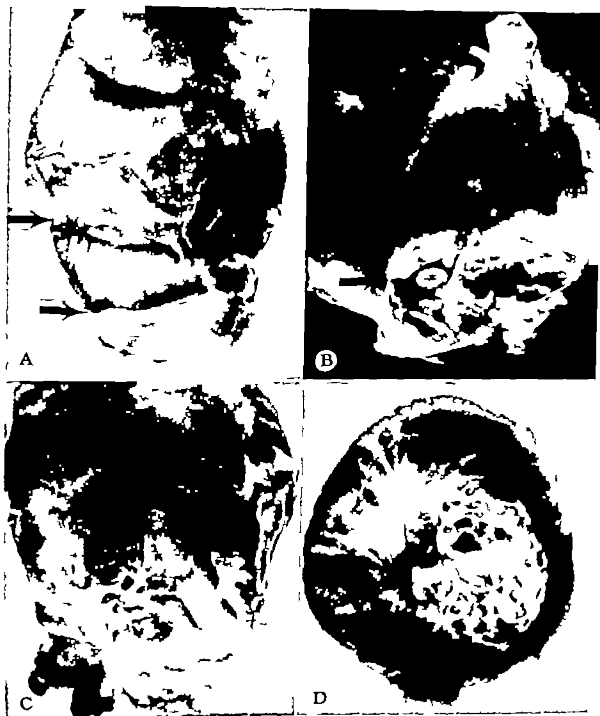


Fig. 3. Macroscopic appearance of heart after ventricular ligature. *A*, The ligature was originally placed at the point indicated by the upper arrow but became gradually displaced to the level of the lower arrow. Between these two levels is the newly formed membranous ventricular wall whose inner surface becomes ossified. The apex of the heart consists of inflammatory granuloma surrounding residual necrotic cardiac muscle debris. *B*, Inner surface of the same heart with hypertrophic papillary muscles above and white ossified or cartilaginous tissue below the level of the ligature (*arrow*). *C*, Similar preparation in which ossification (*white areas*) of papillary muscles is spread slightly above the level of the ligature. (Remnants of black thread still visible in lower left corner.) *D*, Extensive fibrosis with ossification and formation of cartilage on the inner surface of the newly formed cardiac apex, viewed here from above.

osseous plates underneath the endocardial surface These structures were virtually limited to that portion of the heart which was situated below the ligature and no longer contained normal muscle (Fig 3)

Histologic study of the rats killed after 30 days revealed only intense proliferation of elastic tissue underneath the endocardial surface in the connective tissue scar below the ligature. Conversely in the rats killed after 60 days, the formation of cartilage and bone was always manifest.

As far as can be judged from the histologic appearance of the hearts, the first step toward osseous metaplasia is the transformation of fibroblasts into cartilage cells. The spindle-shaped connective tissue cells situated between the thick lamellae of subendocardial elastic tissue become swollen and gradually transform themselves into chondrocytes. Simultaneously wherever this process is underway the elastic tissue loses its structure and stainability so that it comes to resemble cartilage matrix Then the largest chondrocytes begin to degenerate and make space for the invasion of vessels, and the initiation of typical endochondral ossification commences. After a period of growth and remodeling the original bone spicules are transformed into fairly regular bone shells which line the inner surface of the newly formed membranous part of the heart. They usually consist of two solid plates separated by osseous spicules and bone marrow thus simulating the general structure of diploë (Fig 4 *A B* and *C*)

Outside of this bony cup the bulk of the newly formed membranous portion of the heart is made up of connective tissue with unusually numerous and extraordinarily thick walled blood vessels. The media of the arteries may be so intensely developed that the vessels come to resemble sphincters in arteriovenous shunts. The walls of these arteries consist mainly of very hyperplastic smooth muscle cells separated from each other by a reticulum of thick elastic fibers. The latter do not form any distinct lamina but penetrate between the individual smooth muscle fibers so that these come to lie in individual elastic sheaths. Often this process results in the complete obliteration of the arterial lumen (Fig 4 *D* and *E*)

Occasionally we have also seen massive deposition of iron in phagocytes of the parietal connective tissue membrane (Fig 4 *F*) This local siderosis was sometimes followed by amorphous calcification with out ossification in the vicinity of the newly formed bone spicules. However these degenerative changes may merely represent nonspecific consequences of local injury they do not appear to play an integral part in the initiation of ossification

During the final stages, the entire apical portion of the heart is transformed into a connective tissue membrane lined by a rigid cup of flat bone

Discussion

Ossification of the myocardium although unusual is by no means a great rarity Numerous instances of its spontaneous occurrence in man have been described[1-4] but its pathogenesis remains obscure

Ribbert[3] paid special attention to subendocardial and valvular ossification and expressed the opinion that this process does not represent a true metaplasia He believed that, in patches of sclerosis, a very cellular tissue develops, in which first, bone marrow appears, perhaps owing to colonization from the blood and then presumably under the influence of these bone marrow cells indirect metaplasia ensues secondarily Although hemopoietic tissue is not uncommon in ossified plaques within the heart or the large vessels of man[5] its primary function in the process of ossification remains in doubt.

Finestone and Geschickter[6] formulated a theory according to which diminution of the blood supply predisposes to calcification and if circulation subsequently improves (e.g owing to increased vascularity induced by a local inflammatory reaction) ossification of the calcified area results. In fact these authors believe that an excess of calcium and an adequate blood supply are the only factors necessary for the formation of bone in mesenchymal tissue.

The formation of bone in skeletal muscle is much more common especially as seen in the various forms of myositis ossificans. Here mechanical injury is thought to play an important role at least in the traumatic variants, such as rider's bone

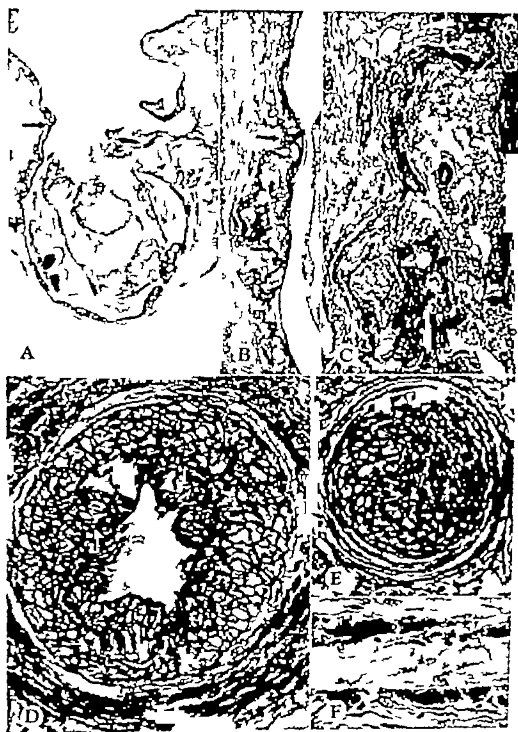


Fig. 4. Microscopic appearance of heart after ventricular ligature. A, General view of section through the newly formed apex of the heart. The inner surface of the connective tissue membrane is lined by osseous plates. (Periodic acid-Schiff ×9.) B, Higher magnification of the portion marked by arrow in A. (Periodic acid-Schiff ×35.) C, Portion marked by arrow in B. Here hemopoietic and fatty bone marrow formation between bony plates is clearly visible. (Periodic acid-Schiff ×120.) D and E, Arteries with characteristic hyperplasia of smooth muscle cells and reticulum of elastic fibers showing partial (D) or complete (E) occlusion of the lumen. (Multipurpose polychrome stain ×460.) F, Iron storage in phagocytes within connective tissue of newly formed ventricular wall. (Prussian blue reaction; ×460.)

and ossification is sometimes preceded by cartilaginous metaplasia of the connective tissue between the muscle bundles.[8] Yet other factors must also play a role since only a few patients respond to muscle injuries with the local formation of bone and despite many attempts it has still not been possible to reproduce myositis ossificans with any degree of regularity in animals.

It may be significant that the osteogenesis experimentally induced either by the tissue scaffolding or the cardiac ligature technique occurs in inflamed connective tissue adjacent to striated muscle (skeletal in the first case and cardiac in the second) but it remains to be seen whether there is any fundamental relationship between these experimental forms of ectopic ossification and clinical myositis ossificans. In any event, the regularity with which the cardiac ligature causes the formation of bone provides us with an experimental model which may prove to be helpful in future studies on the basic mechanisms underlying these forms of metaplasia.

Recent studies with the electron microscope suggest that certain types of hyperplastic arteriolar scleroses induced by hypertension are due to the proliferation of smooth muscle (rather than of endothelial or connective tissue cells) in the arterial walls.[9,10] In the rats bearing the cardiac ligature, the hyperplasia of the smooth muscle cells is so intense that it can readily be demonstrated even with the light microscope however the pathogenesis of this change and of the accompanying proliferation of elastic tissue awaits further elucidation

Summary

Complete occlusion of the apical part of both ventricles by a constricting ligature placed around the heart at the level of the border line between the middle and lower thirds of the ventricles is compatible with survival in the rat. This operation is regularly followed by the induction of bone, bone marrow and cartilage in the membranous scar tissue that develops below the ligature.

At the same time the arteries in the adjacent connective tissue become greatly thickened and sometimes totally occluded by proliferating smooth muscle cells and elastic tissue

This form of cartilaginous and bony metaplasia is preceded by an intense proliferation of the subendocardial elastic tissue Presumably direct metaplasia of fibroblasts into chondrocytes between the elastic tissue lamellae provides the matrix for subsequent endochondral ossification

REFERENCES

1. Selye, H Lemire, Y and Bajusz, E. Induction of bone, cartilage and hemopoietic tissue by subcutaneously implanted tissue diaphragms, Wilhelm Roux Arch. Entwickl Mechanik Organis 151:572, 1960.
2. Selye, H Grasso, S., and Gentile, G. Ossifikatsiia, serdtsa, vyzvannaia khirurgicheskim vmeshatelstvom Eksper Khir 6:22, 1961
3. Selye, H The mast cells, Washington D C. 1965 Butterworth Inc.
4. Gould, S. E. Pathology of the heart, ed. 2 Springfield, Ill., 1960, Charles C Thomas, Publisher
5. Ribbert, H Die Erkrankungen des Endokards, *In* Henke, F and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie. Vol. II Herz und Gefässe, Berlin 1924 Springer Verlag, pp. 184-289
6. Firestone A. J and Geschickter C. F Bone formation in the heart, Am. J Clin. Path. 19:974 1949
7. Barr D P Pathological calcification, J Missouri M. A. 27:593 1930.
8. Giraud, P Bernard R Laval, P and Sanset M: Considérations sur la pathogénie de la myosite ossifiante. À propos d'un cas avec examen anatomique de tous les organes, Semaine hôp. Paris 23:617 1947
9. Spiro, D Lattes, R. G and Wiener J The cellular pathology of experimental hypertension, Am. J Path. 47 19 1965.
10. Haust, M D More, R. H and Movat, H Z The role of smooth muscle cells in the fibrogenesis of arteriosclerosis, Am J Path 37:377 1960.

Deceleration of the heart by alternating current

A new experimental technique

*Armand A. Lefemine, M.D.**
Boston, Mass.

This communication introduces a technique for slowing heart rate by the application of alternating current to the heart via endocardial or epicardial electrodes. Frequencies of 1 to 10,000 cycles per second were used in a continuous or intermittent manner.

Methods and findings

All experiments have been performed upon mongrel adult dogs anesthetized with intravenous pentobarbital and ventilated with an automatic respirator. A femoral artery was cannulated for continuous measurement of intra-arterial pulse pressures, using a Statham strain gauge and a multichannel recorder. The electrocardiogram or electrical oscillations were recorded from standard limb leads. A thoracotomy allowed placement of epicardial or myocardial electrodes and permitted manual guidance of cardiac catheters introduced through the right jugular vein.

Early experiments consisted of holding two plate electrodes manually on each side of the heart. Alternating electrical current was supplied from a low-frequency oscillator with an output of 20 volts open circuit or 10 volts into a 600-ohm rated load. The frequency, wave pattern, voltage, and amperage were verified continuously on a Tektronix oscilloscope. Synchronization of a short burst of this energy with the R wave of the electrocardiogram or the pulse pressure wave was accomplished using a unit originally designed for counterpulsation. Intracardiac bipolar catheters with the electrical poles at distances of 3 centimeters were constructed from commercially available polyethylene-covered wire.

Results

Initial observations applying low-frequency electrical current to the heart through two epicardial plate electrodes revealed that (1) aortic pulsations were reduced by approximately one half and (2) the pulse pressure was increased approximately four times with significant elevations of systolic pressure (Fig. 1). Control rate and blood pressure returned immediately when the current was removed.

Synchronization of a burst of the alternating current approximately 160 milliseconds in duration with the R wave of the electrocardiogram or the pulse pressure wave of the intra-arterial tracing resulted in a reduction in the heart rate by 50 per cent. The electrical current was timed to fall in the location of the T wave, producing a prolonged refractory period and elimina

This study was carried out with the support of National Institutes of Health Grant No. [illegible].
Received for publication May 2, 1966.
*Instructor in Surgery, Harvard Medical School; Associate in Surgery, Peter Bent Brigham Hospital, Boston, Mass. Present address: 85 Jefferson St., Hartford, Conn., 06105.

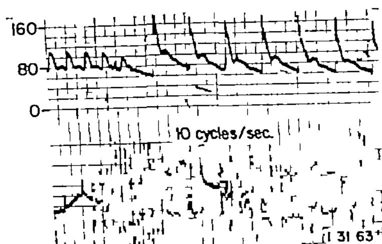


Fig. 1 Ten-cycle/sec. current applied to the heart through epicardial plate electrodes continuously. The rate is approximately half and the pulse pressure reveals fourfold increase.

tion of each alternate electrical and mechanical beat (Figs. 2 and 3). Compensatory increases in pulse pressure were noted.

Intracardiac stimulation required bipolar stimulating catheters having poles 3 centimeters apart (Fig. 4). Endocardial stimulation of the right ventricle or right atrium produced effects similar to those obtained with epicardial electrode plates. The position of the electrode in the ventricle or atrium was not critical.

Left ventricular pressure tracings obtained during continuous stimulation of the right atrium by an endocardial catheter revealed a variety of contractile patterns in response to changes in frequency or voltage of the stimulating current. The frequency could be adjusted so that resulting ventricular rhythm was perfectly regular although at a slower rate (Fig. 5) with a single small ineffective beat between the major contractions. This suggests that the heart was actually being paced by the current so adjusted that the frequency was exactly right for the inherent sinus rate. This is similar to tracings obtained by paired pulsing. Here the similarity ends since it is produced by a continuous current having a frequency of thirty times the sinus rate of the heart. If the frequency could not be adjusted to produce a regular rhythm the ventricular rate differed from the aortic rate in that ineffective ventricular contractions occurred between those pro-

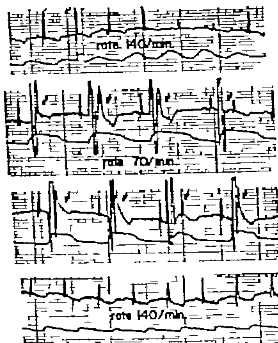


Fig. 2 Synchronization of 10-cycle/sec. alternating current (1.5 volts) with the R wave of the electrocardiogram. The short burst of current is timed to fall in the position of the T wave. Rate is reduced 50 per cent by eliminating alternate beats.

ducing changes in aortic pressure (Fig 6) At times a bigeminal pattern was produced in the aortic pressure (Fig 7)

Increasing the level of energy of the stimulating current above the threshold level needed to produce bradycardia had no real advantage and always increased the danger of ventricular fibrillation (Fig 8) The occurrence of this arrhythmia was always associated with the use of excessive energies. Of interest was the fact that slight increases in energy at times would increase the bradycardic effect without adding to the dangers of arrhythmia (Fig 5) Five dogs were stimulated continuously for 5 hours at threshold levels for producing a bradycardic effect without ventricular fibrillation or tachycardia or significant changes in the threshold levels. The average volts and amperes used in this group are listed in Table I

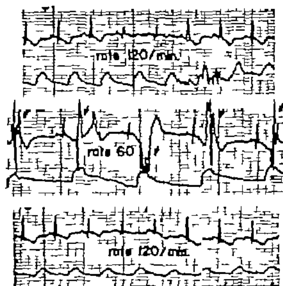


Fig 3 Synchronization of 300-cycle/sec. alternating current (15 volts) with the pulse pressure curve. Th electrical impulse occurs at the position of the T w ve nd reduces the rate 50 per cent.

The frequency of the current and the levels of energy required to produce an effect were related A frequency range from 1 cycle per second to 10 000 cycles per second was found to be effective Above a frequency of 100 cycles per second the threshold levels of energy rose (Fig 9) Any level of frequency in the effective range could be made to produce an effect without the hazard of ventricular fibrillation if threshold levels were not exceeded This includes 60-cycle-per-second current. If the frequency of the current is maintained below 100 cycles per second levels of energy rarely exceeded 4 volts and 4 milliamperes. Serious arrhythmias were not encountered below the level of 10 volts and 10 milliamperes.

Discussion and conclusions

Electrical control of tachycardias would be a valuable technique were it simple and safe Although there is no precedent for the use of alternating current as described in the present technique the use by DeBoer[1] in 1915 and later by Lopez, Edelist and

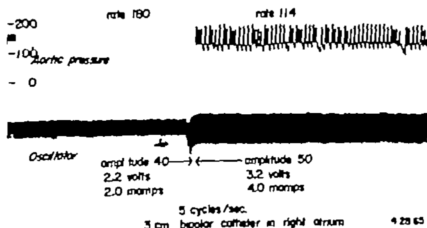


Fig 4 Bradycardia produced by a right atrial endocardial catheter using 5-cycle/sec. current.

Katz,[1] of long pulses to stimulate the atrium approaches this. The technique presented in this communication does have the virtue of simplicity since it is effective with the use of an atrial or a ventricular catheter that can be placed without the necessity of fluoroscopic control and electrical current that can be applied by synchronization with the R wave of the electrocardiogram to reduce heart rate by 50 per cent.

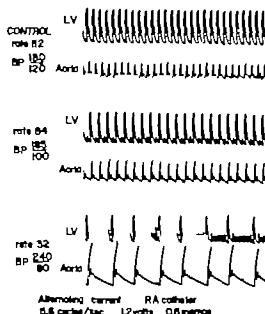


Fig. 5. Effect of continuous stimulation of the right atrium by endocardial catheter at frequency of 5.6-cycles/sec. The frequency was selected to produce this regular effect. A slight increase in current above the threshold level produced even more marked bradycardia of 32 per minute.

Of interest is the fact that alternating current can be used continuously over a wide range of frequencies to stimulate the right atrium or right ventricle. Although many frequencies up to 10 000 cycles per second can be used to produce the same effect in a relatively safe range of energy, the lower frequencies of 5 to 100 cycles per second have the advantage of requiring less energy to produce the desired effects and thus offer a greater margin of safety. The incidence of ventricular fibrillation with this technique has not been completely determined, although experimentally it is nonexistent at threshold levels when stimulation is used continuously for 5 hours. It has been a definite hazard when voltage greatly in excess of threshold levels *has been used. Levels of energy below 10* volts and 10 milliamperes have been found to be free of ventricular fibrillation or serious arrhythmias. The changes in rate and blood pressure are instantaneous when stimulation is applied and revert to control levels immediately when the current is turned off. The mechanism by which this form of electrical stimulation acts is not clear. The synchronized bursts of stimuli to the atrium or ventricle very likely produce depolarization as soon as the refractory period from the preceding normal depolarization is ended. The continuous stimulation by alternating current may produce a regular ventricular response in the manner of paired pulses, although the

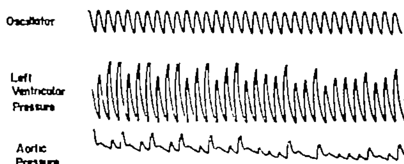


Fig. 6. Continuous endocardial stimulation by left atrial catheter showing an irregular response to the current. The left ventricular tracing reveals varying response only a portion of which is transmitted to the aortic pressure.

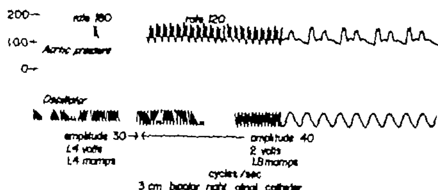


Fig Continuous right trial stimulation by an endocardial electrode producing a bigeminal hythm in the aortic pressure as w ll as slowing of heart rate.

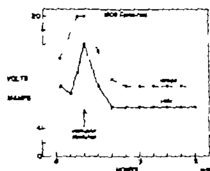


Fig 8 Single experiment showing the occurrence of entricular fibrillation when current was increased w ll abov threshold levels. The dog tolerated continued stimulation at threshold levels for an dditional 4 hours w thout further episodes.

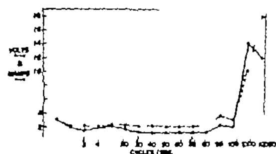


Fig 9 Relationship of threshold lev ls of energy for producing slowing of the heart rate t the frequency of the stimulating current.

frequency of the stimulation is many times that of the atrium or ventricle.

Summary

Low-frequency alternating current has been used to slow the heart rate using endocardial catheter stimulation of the right atrium or right ventricle Frequencies of 1 to 10 000 cycles have been found to be effective Synchronization of a l urst of the alternating current in the region of the S-A node can be used to reduce the heart rate 50 per cent. Continuous stimulation of the atrium or ventricle has also been used to produce bradycardia although this may produce an irregular response with multiple ineffective ventricular beats.

Table I

Average		*Range*	
Volts	*Milliamperes*	*Volts*	*Milliamperes*
2 35	1 4	2 4 3 2	1 0 3 0
2 1	1 1	1 4 3 2	6 2 2
1 0	34	8–2 6	18–1 4
1 5	8	7 2 6	3 1 6
1 2	6	1 0-1 8	2 1 1

0-10 cy les per second

REFERENCES

1 DeBoer S. \ quoted in Cranfield, P F The force of cont action of extrasystoles and the pote tiation of force of the postextr systolic contraction—A historical review Bull New York Acad Med. 41:419 1965.

2. Lopez, J F Edelist A nd Katz, L N Slowing of the heart rat by artificial electrical stimulation with pulses of long duration in the dog. Circulation 28 759 1963

Effect of propranolol, a beta-adrenergic antagonist, on blood flow in the coronary and other vascular fields

*Winifred G. Nayler, D.Sc.**
I. McInnes, F.R.C.S., F.R.A.C.S.
J. B. Swann, M.B., B.S.
Valerie Carson, M.Sc.
T. E. Lowe, D.Sc., M.D., F.R.C.P., F.R.A.C.P.
Melbourne, Australia

Considerable evidence has accumulated which shows that propranolol (1-isopropylamino-3-(1-naphthyloxy)-2-propanol HCl, Inderal) blocks the positive chronotropic and inotropic actions of isoproterenol, epinephrine, and stellate ganglion stimulation on the heart and the vasodilator effect of isoproterenol on the systemic vasculature.[1-3] Therefore, in accordance with Ahlquist's dual receptor hypothesis, propranolol, like pronethalol (Nethalide), may be classified as a sympathetic β-receptor antagonist. Interest already has been displayed in the possible therapeutic use of such β-adrenergic antagonists in the treatment of angina pectoris[4] and in the treatment of certain cardiac arrhythmias,[5-] including those due to cardiac glycoside intoxication.[-11]

Alpha- and β-adrenergic receptors are widely distributed throughout the vasculature, including that of the coronary circulation.[12,13] The establishment of β-adrenergic blockade might therefore result in an altered regional distribution of blood in the systemic circulation. The following experiments were planned to investigate the effect of propranolol on the regional distribution of blood in dogs on heart-lung bypass, with particular attention being given to the effect of this drug on blood flow throughout the coronary circulation. In addition, the direct action of propranolol on myocardial contractions was studied.

Materials and methods

Dogs on heart-lung bypass, perfused under conditions of either constant flow or constant perfusion pressure as required, were used to investigate the effect of propranolol on the systemic circulation.

Dog heart-lung bypass preparations.

ANESTHESIA. Dogs were premedicated with 30 mg. of morphine sulfate (intramuscularly) approximately 1 hour before anesthesia was induced with sodium thiopentone (20-30 mg. per kilogram intravenously). A surgical level of anesthesia was maintained throughout the experiment by giving small supplementary doses of

From Baker Medical Research Institute, Victoria, Australia.
This work was carried out during the tenure of a grant-in-aid from the National Heart Foundation of Australia.
Received for publication May 14, 1966.
*Address: Baker Medical Research Institute, Commercial Road, Prahran S.1, Victoria, Australia.

thiopentone from time to time as required Ventilation was maintained with oxygen delivered from a positive pressure respirator through an endotracheal tube at a rate of 2 liters per minute

A MEASUREMENT OF CORONARY RENAL SPLANCHNIC SUPERIOR VENA CAVAL, INFERIOR VENA CAVAL AND AZYGOS BLOOD FLOW AND SYSTEMIC PERFUSION PRESSURE. The method used has been described previously Anesthetized healthy mongrel dogs (15 to 20 kilograms) were heparinized (2 mg per kilogram per hour intravenously) and placed on heart lung bypass using a Kay Cross disc oxygenator The vascular system was perfused by means of a non pulsatile (Mono) pump through the right common carotid artery at a constant flow rate which varied between 100 and 120 ml per kilogram per minute in different experiments. Appropriate cannulation allowed the independent measurement of venous outflows from the splanchnic renal lower inferior vena caval (IVC) superior vena caval (SVC) and azygos fields and coronary sinus

Blood flow through a particular organ or vascular field was measured as previously described by clamping the connection between the particular collecting cylinder and the reservoir and repeatedly measuring the time required to collect 100 ml of blood Blood flow in a particular field was calculated from the mean results of at least four consecutive collection periods. After each collection period the clamp was released and the collected blood was allowed to drain by gravity into the venous reservoir Preliminary experiments showed that pressure in the cannulated venous segments did not change during the collection procedure Changes in flow due to the opposing pressure head developed during collection of blood in the collecting cylinders were therefore, considered to be negligible for the purposes of these experiments. Samples of arterial and coronary sinus blood were taken as required to estimate the percentage O saturation This was determined spectrophotometrically by a modification of the method of Roos and Rich.[11] Mean systemic perfusion pressure was indicated by a mercury manometer connected to a cannula inserted into the right femoral artery

Unless otherwise stated the hearts beat spontaneously and were not paced In 5 experiments cardiac rate was controlled by electrical stimulation through two wires attached to the anterior surface of the right ventricle The stimuli were pulses of 1 msec. duration delivered from a Tektronix waveform and pulse generator (Type 160 161) at approximately twice the threshold voltage the frequency of stimulation remaining constant throughout each particular experiment. In 3 other experiments the ventricle was made to fibrillate by applying 10 volts of direct current between two points on the anterior surface of the heart.

B MEASUREMENT OF CORONARY BLOOD FLOW AND SYSTEMIC PERFUSION PRESSURE. In these experiments, only mean arterial perfusion pressure and coronary sinus blood flow were measured Anesthetized heparinized mongrel dogs (15 to 20 kilograms) were placed on heart lung bypass as follows

Through a lateral incision in the neck a common carotid artery was dissected out and prepared for cannulation after which thoracotomy was performed using a longitudinal sternal-splitting incision Tapes then were passed around the SVC and IVC and the azygos vein dissected clean after which the pericardium was opened and a tape passed around the pulmonary artery The right femoral artery was then cannulated and connected to a mercury manometer used to detect mean systemic pressure

With the use of a wide bore metal cannula the common carotid artery was cannulated and the cannula was connected to the inflow lead of the nonpulsatile (Mono) pump Next with the use of a No 26 Bardic catheter the SVC was cannulated through the proximal stump of the azygos vein after which a No. 28 Bardic catheter was inserted via the right atrial appendage into the IVC and the tip of the catheter was located immediately above the diaphragm

After appropriate connection of the cannula the tapes around the SVC and IVC cannulae were tightened and total bypass was begun the heart lung machine having been primed with 1 liter of homologous heparinized blood and 1.5 liters of equal

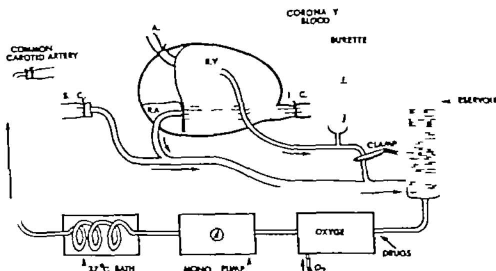


Fig 1 Schematic representation of apparatus used to measure coronary blood flow in dog heart-lung bypass preparation. *IVC* Inferior vena cava. *SVC* Superior vena cava. *PA* Pulmonary artery *RA* Right atrium *RV* Right ventricle.

parts of aqueous solutions of 5 per cent dextrose and 0 9 per cent \aCl aerated with 100 per cent O in the disc oxygenator

Coronary cannulation was effected by placing a purse-string suture in the wall of the right ventricle and inserting a No 22 Bardic catheter through a small ventriculotomy into the cavity of the right ventricle. This catheter was then connected to a graduated burette which in turn was connected to the venous reservoir of the heart-lung machine The tape around the pulmonary artery was tightened and coronary blood flow was measured by repeatedly determining the time required for the collection of 100 ml of blood in the burette. The perfusion system is shown schematically in Fig 1

Dog papillary muscle p eparations The direct effect of propranolol on cardiac contractions was determined through the use of small papillary muscles excised from freshly exsanguinated dogs. Isolated papillary muscles were suspended isometrically n aerated (95 per cent O + 5 per cent CO) Tyrode solution which was maintained at 37°C. and had the following composition n millimoles—NaCl 130 KCl 5 6 CaCl 1 6 NaHCO₃, 25 0 sucrose 13 1 glucose, 11 1 NaH PO₄, 9 1 MgSO₄, 1 14—and was prepared from Merck analytical reagent grade chemicals dissolved in all-glass distilled water Isometric conditions were maintained by applying 5 grams of tension. Stimulation was effected with suprathreshold rectangular pulses of 10-msec duration delivered from a Tektronix pulse generator at a rate of 60 pulses per minute Contractions were detected with four microsensor semiconductor strain gauges (Type MS132 120) arranged to form a Wheatstone bridge the output of this bridge was displayed on an ultraviolet light photographic recorder Each preparation was equilibrated in Tyrode solution for 60 minutes prior to the addition of drugs.

DRUGS The following drugs were used sodium thiopentone,** propranolol *** isoproterenol † epinephrine,‡ norepinephrine,§ angiotensin I and dipyridamole.

Drugs were added directly to the arterial line of heart-lung bypass preparations. When added to provide concentrations in excess of 0.2 mg per kilogram propranolol was added slowly by means of an infusion pump # Dilutions of drugs were prepared

*S. E. Laboratories, Type 200 R.
**Pentothal, May and Baker Ltd Australia.
***Inderal, I.C.I. (Australia), Imperial Chemical Industries, England.
†Isuprel, Winthrop Laboratories, Australia.
‡Epinephrine tartrate, David Bull & Co., Australia.
§Levophed bitartrate Winthrop Laboratories, Australia.
||Hypertensin, Ciba, Basle
¶Persantin, Boehringer-Ingelheim, Ltd., Germany
#Harvard Apparatus Co., Inc., Model 600-910.

thiopentone from time to time as required Ventilation was maintained with oxygen delivered from a positive pressure respirator through an endotracheal tube at a rate of 2 liters per minute

A MEASUREMENT OF CORONARY RENAL, SPLANCHNIC SUPERIOR VENA CAVAL, INFERIOR VENA CAVAL, AND AZYGOS BLOOD FLOW AND SYSTEMIC PERFUSION PRESSURE. The method used has been described previously [14] Anesthetized healthy mongrel dogs (15 to 20 kilograms) were heparinized (2 mg per kilogram per hour intravenously) and placed on heart lung bypass using a Kay-Cross disc oxygenator The vascular system was perfused by means of a non pulsatile (Mono) pump through the right common carotid artery at a constant flow rate which varied between 100 and 120 ml per kilogram per minute in different experiments. Appropriate cannulation allowed the independent measurement of venous outflows from the splanchnic renal lower inferior vena caval (IVC) superior vena caval (SVC) and azygos fields and coronary sinus.

Blood flow through a particular organ or vascular field was measured as previously described [14] by clamping the connection between the particular collecting cylinder and the reservoir and repeatedly measuring the time required to collect 100 ml of blood Blood flow in a particular field was calculated from the mean results of at least four consecutive collection periods. After each collection period the clamp was released and the collected blood was allowed to drain by gravity into the venous reservoir Preliminary experiments showed that pressure in the cannulated venous segments did not change during the collection procedure. Changes in flow due to the opposing pressure head developed during collection of blood in the collecting cylinders were therefore considered to be negligible for the purposes of these experiments. Samples of arterial and coronary sinus blood were taken as required to estimate the percentage O_2 saturation This was determined spectrophotometrically by a modification of the method of Roos and Rich [15] Mean systemic perfusion pressure was indicated by a mercury manometer connected to a cannula inserted into the right femoral artery

Unless otherwise stated the hearts beat spontaneously and were not paced In 5 experiments, cardiac rate was controlled by electrical stimulation through two wires attached to the anterior surface of the right ventricle The stimuli were pulses of 1 msec. duration delivered from a Tektronix waveform and pulse generator (Type 160 161) at approximately twice the threshold voltage, the frequency of stimulation remaining constant throughout each particular experiment. In 3 other experiments the ventricle was made to fibrillate by applying 10 volts of direct current between two points on the anterior surface of the heart.

B MEASUREMENT OF CORONARY BLOOD FLOW AND SYSTEMIC PERFUSION PRESSURE In these experiments, only mean arterial perfusion pressure and coronary sinus blood flow were measured Anesthetized heparinized mongrel dogs (15 to 20 kilograms) were placed on heart lung bypass as follows

Through a lateral incision in the neck a common carotid artery was dissected out and prepared for cannulation after which thoracotomy was performed using a longitudinal sternal-splitting incision. Tapes then were passed around the SVC and IVC and the azygos vein dissected clean after which the pericardium was opened and a tape passed around the pulmonary artery The right femoral artery was then cannulated and connected to a mercury manometer used to detect mean systemic pressure

With the use of a wide bore metal cannula the common carotid artery was cannulated and the cannula was connected to the inflow lead of the nonpulsatile (Mono) pump Next with the use of a No 26 Bardic catheter the SVC was cannulated through the proximal stump of the azygos vein after which a No 28 Bardic catheter was inserted via the right atrial appendage into the IVC and the tip of the catheter was located immediately above the diaphragm

After appropriate connection of the cannula the tapes around the SVC and IVC cannulae were tightened and total bypass was begun the heart lung machine having been primed with 1 liter of homologous heparinized blood and 1.5 liters of equal

Table I Effect of 0 15 to 5.0 mg /Kg of propranolol on mean systemic perfusion pressure and regional blood flow in dog heart-lung bypass preparations perfused under conditions of constant flow

Preparation number	Propranolol	Perfusion pressure (mm Hg)	Regional blood flow (ml./min)					
			Coronary	Splanchnic	Renal	SVC	IVC	Azygos
1	Before	90	194 ± 0	626 ± 0	226 ± 0.5	910 ± 0	571 ± 1	264 ± 0
	After 0 15 mg /kg	95	169 ± 1	491 ± 0.5	175 ± 0	935 ± 0	625 ± 0	265 ± 0
2.	Before	95	270 ± 0	900 ± 0.5	375 ± 0	697 ± 1	496 ± 2	294 ± 0
	After 0.15 mg /kg	110	206 ± 1	625 ± 1	235 ± 0	910 ± 0	572 ± 1	295 ± 1
3	Before	80	240 ± 0.5	1,090 ± 0	212 ± 1	414 ± 2	585 ± 1	295 ± 2
	After 0.2 mg /kg	90	218 ± 0 5	833 ± 2	188 ± 0	546 ± 1	640 ± 1 5	310 ± 2
4	Before	80	240 ± 0	840 ± 1	234 ± 0.5	545 ± 0.5	565 ± 2	395 ± 1 5
	After 0.5 mg./kg	95	200 ± 1	666 ± 1.5	195 ± 1	631 ± 1	590 ± 2	420 ± 2
5	Before	90	266 ± 0.5	965 ± 0	226 ± 1.5	690 ± 0	465 ± 1	312 ± 0
	After 0.5 mg./kg	110	229 ± 1 5	682 ± 2	175 ± 0	808 ± 2	550 ± 2	320 ± 0
6.	Before	100	303 ± 0	617 ± 1	193 ± 1	588 ± 1	545 ± 2 5	305 ± 1
	After 5 0 mg /kg	115	183 ± 0	475 ± 1	171 ± 0.5	681 ± 2	600 ± 1	320 ± 0

Perfusion pressure and flows recorded after the addition of propranolol refer to the maximum sustained effect. Heart rate was not controlled during these experiments. Each listed flow value is the mean (plus scatter) of four consecutive measurements made when the maximum effect of propranolol was apparent.

and listed in Table I were obtained from the other 8 preparations in which conditions of constant flow were maintained throughout the experiment. Variable effects were recorded from the azygos circulation In 10 of 15 preparations the addition of propranolol resulted in a slightly increased azygos flow but in the other 5 preparations the azygos flow remained unchanged

Changes in regional blood flow and systemic perfusion pressure caused by a single dose of propranolol persisted for approximately 40 to 60 minutes, after which the measured parameters gradually returned to their initial control levels. If after these initial control levels were reestablished a second dose of propranolol was given then the changes in perfusion pressure and regional blood flow which occurred were not significantly different from those which occurred after the initial addition of the same concentrations of propranolol

The addition of propranolol to provide these same concentrations in 5 other preparations in which the heart rate was controlled and in 3 preparations in which fibrillation had been established resulted in a decreased coronary flow similar to that already described for those preparations in which the heart rate was not regulated The decline in coronary sinus blood flow recorded after the addition of propranolol to 2 typical heart lung bypass preparations in which the heart rate was regulated is shown by the data listed in Table II The addition of less than 0 10 mg per kilogram of propranolol failed to cause any significant change in regional blood flow in these preparations.

To determine the effect of propranolol on the resistance to blood flow in the various vascular beds other preparations were used in which throughout the experiment perfusion pressure was maintained at the initial control level by adjusting the output of the perfusion pump. The results in 4 such preparations are summarized in Table III and show that under conditions of constant perfusion pressure 15 to 0

Table II Effect of 0.15 to 5.0 mg./Kg. of propranolol on oxygen saturation of coronary blood in dogs on heart-lung bypass perfused under conditions of constant flow

Preparation number	Heart rate	Propranolol	Per cent oxygen saturation: Arterial	Per cent oxygen saturation: Coronary sinus blood	Coronary blood flow (ml./min.)
16	Not regulated	Before	100	68	177 ± 0.5
		After 0.15 mg./Kg.	100	78	150 ± 1
		After 2.0 mg./Kg.	100	88	111 ± 0
17	Not regulated	Before	98.5	89.5	208 ± 1
		After 0.15 mg./Kg.	98.5	96	192 ± 2
		After 0.5 mg./Kg.	98	95	174 ± 0
21	Controlled (180/min.)	Before	100	76	212 ± 1
		After 0.2 mg./Kg.	100	84	180 ± 1.5
22	Controlled (180/min.)	Before	99.5	72.5	240 ± 1
		After 5.0 mg./Kg.	99.5	95	160 ± 0

Arterial and coronary sinus blood was sampled for determination of percentage oxygen saturation immediately before injection of propranolol and again during maximum sustained effect of propranolol on coronary blood flow. The listed values for coronary flow are the mean results (plus scatter) of four consecutive measurements of flow made when propranolol was maximally effective.

Table III Effect of 0.15 to 5.0 mg./Kg. of propranolol on regional blood flow in dog heart-lung bypass preparations perfused under conditions of constant perfusion pressure

Preparation number	Propranolol	Perfusion pressure (mm. Hg)	Regional blood flow (ml./min.): Coronary	Splanchnic	Renal	SVC	IVC	Azygos
9	Before	90	170 ± 0	956 ± 1	160 ± 1	320 ± 1	520 ± 1	193 ± 0
	After 0.15 mg./Kg.	90	148 ± 0	740 ± 1	148 ± 1	385 ± 1	610 ± 1	233 ± 0
10.	Before	70	193 ± 0.5	865 ± 2	123 ± 2	540 ± 2	638 ± 0	228 ± 1
	After 0.15 mg./Kg.	70	176 ± 1	714 ± 2	104 ± 1	620 ± 2	692 ± 2	230 ± 0
11	Before	80	200 ± 1	631 ± 0	285 ± 1	810 ± 2	370 ± 1	66 ± 1
	After 0.3 mg./Kg.	80	154 ± 2	468 ± 1	222 ± 1	937 ± 1	615 ± 2	275 ± 2
12.	Before	95	243 ± 1	672 ± 2	231 ± 0	428 ± 1	547 ± 2	246 ± 2
	After 5.0 mg./Kg.	95	136 ± 1.5	518 ± 0	186 ± 1	604 ± 0	627 ± 1	248 ± 1

Perfusion pressure was maintained constant by adjusting the output of the perfusion pump. The maximum sustained effect of propranolol is shown. Heart rate was not controlled. Regional blood flow in a particular field was calculated from the mean of four consecutive measurements.

mg. per kilogram of propranolol caused decreased coronary, splanchnic, and renal blood flow, reflecting vasoconstriction in these vascular fields, and increased IVC and SVC blood flow, reflecting vasodilatation of the IVC and SVC vasculature.

Effect of propranolol on myocardial oxygen usage. Coronary blood flow and the percentage oxygen saturation of arterial and coronary sinus blood were determined before and after the addition of 0.15 to 5.0 mg. per kilogram of propranolol to

the systemic circulation of 7 dog heart lung bypass preparations perfused under conditions of constant flow In 4 of these preparations the heart rate was not regulated and in the other 3 preparations the heart rate was controlled The results from 4 typical preparations are listed in Table II The other 3 preparations provided similar results. In general these results indicate that the propranolol induced decline in coronary blood flow is associated with an increase in the oxygen saturation of coronary sinus blood and therefore with a decline in the amount of oxygen extracted by the heart from coronary blood Similar results were recorded whether the heart was or was not controlled as is shown in Table II and also in other experiments in which 0 15 to 0.5 mg per kilogram of propranolol was added to the circulation of dog heart-lung bypass preparations in which fibrillation had been established

Effect of d pyridamole on coronary blood flow during propranolol induced β-adrenergic blockade In the absence of β-adrenergic blockade the addition of 10 µg per kilogram of isoproterenol to the circulation of dog heart lung bypass preparations perfused under conditions of constant perfusion pressure resulted in a marked increase in coronary blood flow During the present experiments, propranolol induced β-adrenergic blockade was considered to be effective if coronary blood flow remained unchanged after the injection of 10µg per kilogram of isoproterenol During these experiments, 0 15 mg per kilogram of propranolol provided only partial β-blockade and it was necessary to use 0 4 to 0.5 mg per kilogram of propranolol to produce complete β-blockade. The addition of 0.5 mg per kilogram of dipyridamole to such completely β-blockaded preparations consistently resulted in a marked and sustained increase in coronary blood flow The results of such an experiment are displayed in Fig 2 In this particular experiment the heart was stimulated to contract at the controlled rate of 180 beats per minute throughout the entire experiment. The results obtained from 4 other preparations are listed in Table IV Data listed in Table IV show the effect of this same con

Table IV Effect of 0.5 mg /Kg of dipyridamole on coronary blood flow in β-adrenergically blocked heart-lung bypass preparations perfused under conditions of constant perfusion pressure or constant flow

Preparation number	Experiment: Before propranolol		After propranolol (0 4-0.5 mg /Kg)		After propranolol (0 4-0.5 mg /Kg) + d pyridamole (0 5 mg /Kg)	
	Coronary flow (ml./min.)	Perfusion pressure (mm Hg)	Coronary flow (ml./min.)	Perfusion pressure (mm Hg)	Coronary flow (ml /min)	Perfusion pressure (mm. Hg)
Constant perfusion pressure						
11	220	90	154 ± 0 5	90	260 ± 1	90
14	300	90	223 ± 0	90	353 ± 0	90
19	300	90	174 ± 1	90	325 ± 2	90
20.	180	100	129 ± 0	100	262 ± 1	100
Constant flow						
26.	176	110	150 ± 1	120	285 ± 1	110
27	188	100	133 ± 0	110	260 ± 0	100

During these experiments the failure of 1 µg per kilogram of isoproterenol to increase coronary flow was used as a criterion of effective β blockade by propranolol. Coronary flow was calculated from the mean of four consecutive measurements of flow

Table V Effect of propranolol on isometric contractions of dog papillary muscle

Preparation number	Stimulation rate (per minute)	Per cent decline in tension $\left(\frac{A - B}{A} \times \frac{100}{1}\right)$ — Propranolol (µg/mL.) 0.1	0.2	2	4
1	60	16		18	22
2	60	12		26	50
3	60	12		50	70
4	60	6	16		

Where percentage decline in twitch tension is calculated as the difference in tension produced during isometric contractions before (A) and 20 minutes after (B) the addition of propranolol, calculated as percentage relative to the tension produced before propranolol was added. The particular concentrations of propranolol used for each preparation are as shown in the table.

centration of dipyridamole on 2 other β-adrenergically blocked preparations which were perfused under conditions of constant flow and in which no attempt was made to maintain the same perfusion pressure before and after the addition of dipyridamole.

Other experiments showed that the addition of 0.5 to 1.0 mg. per kilogram of dipyridamole 30 minutes after 5.0 mg. per kilogram of propranolol had been added to preparations which were perfused under conditions of constant flow resulted in a marked maintained increase in coronary blood flow, which in some instances was accompanied by a small decline in arterial perfusion pressure.

Effect of propranolol on dog papillary muscle preparations. Isometric contractions recorded from freshly excised papillary muscles which were stimulated to contract once every second remained relatively constant while the muscles were immersed in Tyrode solution. The addition of propranolol to these preparations resulted in a progressive decline in the tension produced during contraction. The results of 4 typical experiments are summarized in Table V and show that 0.15 µg per milliliter of propranolol caused a significant decline in twitch tension in each of the 4 experiments. Table V shows that the immersion of these preparations in Tyrode solution containing more than 0.15 µg per milliliter of propranolol resulted in a decline in the tension produced during regular contractions which exceeded that caused by this minimally effective concentration of propranolol (0.15 µg per milliliter). The negative inotropic effect of propranolol on these muscles was abolished after they had been immersed for approximately 30 minutes in propranolol-free Tyrode solution.

Discussion

These results indicate that the administration of propranolol to dog heart-lung bypass preparations is followed almost immediately by a sustained change in the regional distribution of blood in the systemic circulation. In those experiments which were performed under conditions of constant flow this change in regional blood flow was accompanied by a small but sustained rise in perfusion pressure. Blood flow through the splanchnic, renal, and coronary circulations declined, whereas that through the IVC and SVC vascular fields increased. Similar changes in regional blood flow were recorded in those experiments in which propranolol was injected into dog heart-lung bypass preparations which were perfused under conditions of constant perfusion pressure, from which it can be concluded that 0.15 to 5 mg. per kilogram of propranolol increased the resistance to blood flow in the coronary, splanchnic, and renal circulations and decreased the resistance to blood flow in the IVC and SVC vascular beds, this latter

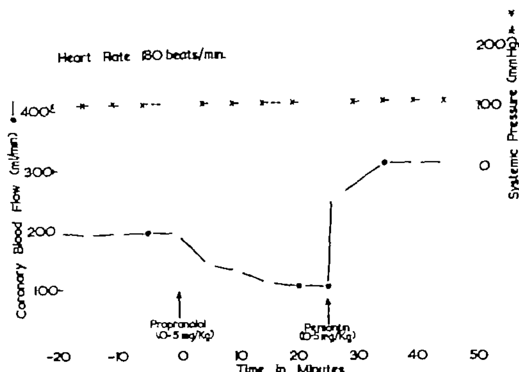


Fig 3 Effect of dipyridamole (Persantin) on coronary blood flow in typical dog heart-lung bypass preparation previously treated with propranolol. Dog heart-lung bypass preparation perfused under conditions of constant perfusion pressure. Propranolol, 0 5 mg./kg was added at arrow as indicated and was followed 25 minutes later by the addition of 0 5 mg /kg. of dipyridamole. The heart was stimulated to contract at constant rat (180 beats per minute) throughout the experiment. Each point on the graph represents the mean of four consecutive measurements of flow made t that particular time.

change reflected an increase in muscle blood flow

Parratt[1] described a decline of 29 per cent in myocardial blood flow in anesthetized dogs after the administration of 5 mg per kilogram of propranolol. The present results confirm Parratt s findings and in add tion indicate that a similar decline in coronary blood flow occurs after the administration of much smaller doses of this drug e.g., 0 15 mg per kilogram of propranolol. This propranolol-induced decline in coronary blood flow occurred whether the heart rate was or was not regulated as is shown by the results listed in Table II and Fig 3. It seems to be unprobable therefore that the decline in coronary blood flow which follows the ad dition of propranolol can be attributed solely to an effect of this drug on heart rate [47]

The present results indicate that the propranolol-induced decline in coronary blood flow is associated with a decrease in myocardial oxygen consumption This decl ne in myocardial oxygen usage by propranolol treated preparations is reflected in the increased oxygen saturation of coronary sinus blood relative to that which existed before propranolol was added to the circulation, and may be related to the effect of the drug on myocardial con tractions. Thus the tension produced by electrically stimulated papillary muscles during isometric contractions declined after propranolol was added to provide a concentration of or in excess of 0 15 µg per milliliter

The results reported in this present study do not permit any conclusion to be drawn as to whether the constrictor effect of propranolol on the coronary splanchnic, and enal vasculature reflects the drug s β-adrenergic blocking properties. There now is abundant evidence which shows that the coronary circulation does contain β-

adrenergic dilator receptors[12] and it is possible that the vasoconstrictor effect of propranolol on the coronary circulation reflects the partial or complete inhibition of such an intrinsic adrenergic dilator mechanism[13] It is difficult, however to account for the vasodilator effect of propranolol on the IVC and SVC circulations in terms of such β-adrenergic blockade

Summary

The administration of 0 15 to 5 mg per kilogram of propranolol to dog heart lung bypass preparations perfused under conditions of constant flow resulted in a small rise in perfusion pressure and marked changes in regional blood flow Blood flow in the coronary splanchnic and renal circulations declined whereas that in the SVC and IVC circulations increased Similar changes in regional blood flow were recorded after the addition of these same concentrations of propranolol to other heart lung preparations perfused under conditions of constant perfusion pressure. Coronary vasoconstriction occurred after propranolol was added whether the heart rate was or was not regulated and whether fibrillation had or had not been established The propranolol induced reduction in coronary blood flow was associated with an increase in oxygen saturation of coronary sinus blood The decrease in oxygen usage by the heart which follows the addition of propranolol may be related to the direct negative inotropic effect of the drug on cardiac muscle

Dipyridamole increased coronary blood flow in the presence of propranolol induced β-adrenergic blockade without effecting any change in systemic perfusion pressure.

Supplies of Inderal were generously donated by Imperial Chemical Industries, England, and supplies of Persantin by Boehringer Ingelheim, Ltd., Germany W gratefully acknowledge the technical assistance of Miss L. Turnbull and Messrs. Breen and Bremner

REFERENCES

1 Black, J W Crowther A F Shanks, R. G Smith, L. H and Dornhorst, A. C. A new adrenergic beta-receptor antagonist, Lancet 1 1080, 1964
2 Black, J W Duncan, W A M and Shanks, R. G. Comparison of some properties of pronethalol and propranolol, Brit. J Pharmacol 25:577 1965.
3 Ahlquist, R. P A study of the adrenotropic receptors, Am. J Physiol. 153:586, 1948.
4 Alleyne, G. A. O Dickinson, C. J Dornhorst, A. C. Fulton, R. M Green, K. G., Hill, I D Hurst, P Laurence, D R., Pilkington, T Pritchard, B N C. Robinson, B., and Rosenheim M L. Effect of pronethalol in angina pectoris, Brit. M J 2 1226, 1963.
5 Benfey B. G., and Varma, D R. Antisympathomimetic and antifibrillatory effects of pronethalol and propranolol, Brit. J Pharmacol. 26:3 1966.
6 Taylor R R., and Halliday E J Beta-adrenergic blockade in the treatment of exercise-induced paroxysmal ventricular tachycardia, Circulation 32 778, 1965.
7 Lucchesi, B. R The action of Nethalide upon experimentally induced cardiac arrhythmias, J Pharmacol. & Exper Therap. 145:286, 1964.
8 Stock, J P P and Dale N Beta adrenergic receptor blockade in cardiac arrhythmias, Brit. M J 2 1238, 1963.
9 Erlij D and Mendez, R. The modification of digitalis intoxication by excluding adrenergic influences on the heart, J Pharm. & Exper Therap. 144:97 1964
10 Vaughan Williams, E. M and Sekiya, A Prevention of arrhythmias due to cardiac glycosides by block of sympathetic β-receptors, Lancet 1 420 1963.
11 Dreifus, L. S., Rabinno, M D and Watanabe, Y Newer agents in the treatment of cardiac arrhythmias, M Clin. North America 48:371, 1964.
12 Zuberbuhler R. C., and Bohr D F Responses of coronary smooth muscle to catecholamines, Circulation Res. 16:431 1965
13 Klocke, F J Kaiser G A Ross, J and Braunwald, E. An intrinsic adrenergic vasodilator mechanism in the coronary vascular bed of the dog, Circulation Res. 16:376 1965.
14 Nayler W G Race, D Price, J M and Lowe, T E. Some effects of cardioactive fraction isolated from human blood on the peripheral circulation, Circulation Res. 18 1 1966.
15 Roos, A., and Rich, J A. Spectrophotometric determination of oxyhemoglobin saturation and oxygen content of blood J Lab. & Clin. Med. 40:131 1952.
16. Parratt, J R. Blockade of sympathetic β-receptors in the myocardial circulation Brit J Pharmacol. 24:601 1965.
17 Parratt, J R., and Grayson, J Myocardial vascular reactivity after beta-adrenergic blockade Lancet 1:338, 1966.
18. Kinsella, D Troup, W and McGregor M : Studies with new coronary vasodilator drug Persantin Am. Heart J 63 146, 1962.
19 West, J W Bellet, S Manzoli, V C. and Muller O F Effect of Persantin (RA8) new coronary vasodilator on coronary blood flow and cardiac dynamics in the dog, Circulation Res. 10:35 1962.

Electrocardiographic changes and oxygen consumption in acute salt depletion

Mohammed A Khoyi M D
Tehran Iran

The effects of variations in the concentration of serum electrolytes particularly calcium and potassium on the form and duration of the various components of the electrocardiogram have been established[13,14,2] Suggestive evidence has been produced that reversible electrocardiographic changes may be associated with fluctuations in serum electrolytes other than potassium and calcium[7,14,15,18] Electrocardiographic changes have also been studied in DOCA or cortisone treated and adrenalectomized animals.[2,15,17] In the latter case in addition to alterations in the concentration of serum sodium there is a marked change in the concentration of serum potassium

Electrocardiographic changes in acute salt depletion which is distinguished by hyponatremia with slight or no change in the concentration of serum potassium[8] have not been studied extensively

In the present work, experimental salt depletion of a rather marked degree was produced in dogs in order to observe the possible ECG changes.

Methods

Forty five dogs 16 to 11 kilograms in weight anesthetized with 30 mg per kilogram of sodium pentobarbital were used for this study Samples of blood were drawn from the femoral vein into dry syringes containing liquid paraffin. Concentrations of serum sodium and potassium were determined using a Beckman flame attachment with Model B spectrophotometer Hematocrits were determined with Wintrobe tubes. Blood pressure in the left carotid artery was recorded with a mercury manometer Oxygen consumption was measured by connecting the trachea to a Sanborn Metabulator Oxygen saturation of the blood was measured in the right ear with a Waters X 70 oximeter The electrocardiogram was recorded with a Sanborn Viscette The three standard and three monopolar limb leads were used Amplitudes of the P and T waves in each lead were measured by two persons from a series of four to five consecutive cardiac cycles.

The experiments were performed on two different groups In Group I 100 to 310 ml. per kilogram (average, 177 ml) of a 5 percent glucose solution was injected intraperitoneally into 27 dogs. In Group II 130 to 206 ml. per kilogram (average 180 ml) of Tyrode solution was injected into 18 dogs in the same way

The animals were kept under light anesthesia for 2 to 5 hours. At the end the measurements were repeated after the evacuation of the peritoneal fluid

From the Department of Experimental Medicine and Pharmacology (Prof N [illegible]) Medical Faculty University of Tehran, Tehran, Iran.
Received for publication April 11, [illegible]
Associate Professor of Experimental Medicine and Pharmacology

Table I

	Group I—Experimental			
	Before injection of glucose ± *SD*	*After jection f glucose* ± *SD*	*Average difference* ± *SD*	*p*
Na (mEq /L)	147 2 ± 5 9 (26)	121 3 ± 12 7	−25 9 ± 11 8	0 001
K (mEq /L.)	5 1 ± 0 8 (9)	4 7 ± 0 7	− 0 39 ± 0 39	0 025
Hematocrit ( )	33 32 ± 5 05 (24)	46 98 ± 7 28	13 66 ± 4 83	0 001
B P (mm. Hg)	103 8 ± 19 2 (25)	79 4 ± 25 8	−24 4 ± 21 8	0 001
O (ml /kg /min)	11 4 ± 3 1 (14)	8 3 ± 1 9	− 3 03 ± 2 96	0 005
P (m)	0 77 ± 0 59 (24)	1 33 ± 0 86	0 55 ± 0 96	0 02
P	2 1 ± 0 69 (24)	3 03 ± 1 31	0 92 ± 1 06	0 001
P	1 49 ± 0 75 (24)	1 55 ± 1 53	0 06 ± 1 58	N S.
P	−1 15 ± 1 07 (21)	−2 25 ± 0 77	− 1 1 ± 1 44	0 005
P	−0 15 ± 0 73 (22)	−0 34 ± 1 13	− 0 19 ± 1 3	N S.
P	1 79 ± 0 64 (22)	2 4 ± 1 35	0 61 ± 1 36	0 05
T	0 55 ± 0 29 (24)	0 51 ± 2 04	− 0 04 ± 1 52	N S
T	1 94 ± 1 42 (24)	4 05 ± 2 15	2 1 ± 1 45	0 001
T	1 70 ± 1 17 (24)	3 44 ± 1 83	1 74 ± 1 28	0 001
T	−1 23 ± 1 06 (21)	−2 36 ± 1 79	− 1 13 ± 1 29	0 001
T	−0 6 ± 0 82 (22)	−1 41 ± 1 52	− 0 81 ± 1 09	0 005
T vr	1 97 ± 1 23 (22)	3 75 ± 1 72	1 77 ± 1 26	0 001

The figures in parentheses indicate the number of animals
N S Not Significant

Results

The results are given in Table I In Group I there was a significant increase in hematocrit and a marked decrease in the concentration of serum sod um with a slight lowering of the level of potassium Arterial blood pressure fell significantly Oxygen consumption decreased 27 per cent in Group I but did not change in Group II The oxygen saturation of arterial blood remained stable during the experi ments. There was a significant increase in the voltage and peaking of the P and T waves in the first group There was no change in these waves in Group II The P R interval QRS interval RS-T junc tion and amplitudes of the R and S waves were normal in both groups.

Discussion

Diffusion of plasma electrolytes (mainly Na Cl and HCO) into the peritoneal fluid results in hypotonicity of the extracellular fluid Osmotic equilibrium between the intracellular and extracellular fluid is brought about by the movement of the extracellular water into the cells. This lowers the volume of extracellular fluid and the blood pressure and increases the hema tocrit. [4 8] Levels of catecholamines in the blood increase, and there is marked adreno-cortical and ADH secretion under these circumstances.

It has been shown that the effect of corticosteroids on the ECG appears after the drug has been administered for several days [9 11] A fall in the concentration of serum potassium would be expected to re-duce the voltage of the P and T waves.[12,13 14] Furthermore, in the present experiments. there was no correlation between the fall in the concentration of potassium and the ECG alterations

The development of a severe acidosis seems to be improbable A 17 per cent de-crease in the total concentration of serum sodium seen in the experimental group would require a decrease of only 4 mEq per liter in plasma bicarbonate Henderson and associates[13] and Reynolds and asso-ciates[14] found no relationship between the level of plasma bicarbonate and the ECG alterations unless the former was accom panied by changes in the level of plasma potassium A linear relationship exists between the concentration of hydrogen ion

Group II—Control

Before injection of Tyrode solution ± SD	*After injection of Tyrode solution ± SD*	*Average difference ± SD*	*p*
145.0 ± 3.0 (18)	146.3 ± 4.9	1.22 ± 3.19	N.S.
3.4 ± 0.7 (14)	3.6 ± 0.7	0.2 ± 0.63	N.S.
30.4 ± 4.5 (16)	32.3 ± 5.4	1.89 ± 2.84	0.025
102.6 ± 16.7 (17)	98.6 ± 21.9	−4.0 ± 17.9	N.S.
11.82 ± 1.56 (16)	12.06 ± 2.47	0.24 ± 2.53	N.S.
0.63 ± 0.64 (17)	0.7 ± 0.51	0.08 ± 0.74	N.S.
2.18 ± 0.97 (17)	1.8 ± 0.8	−0.38 ± 1.01	N.S.
1.78 ± 1.09 (17)	1.0 ± 0.74	−0.76 ± 1.04	0.02
−1.53 ± 0.81 (17)	−0.9 ± 1.42	0.63 ± 1.76	N.S.
−0.56 ± 0.79 (17)	−0.27 ± 0.79	0.29 ± 0.97	N.S.
1.69 ± 0.86 (17)	1.45 ± 0.8[illegible]	−0.24 ± 0.8[illegible]	N.S.
0.25 ± 0.61 (17)	−0.27 ± 0.88	−0.52 ± 0.74	0.0
2.0 ± 0.8 (17)	1.79 ± 1.54	−0.2 ± 1.43	N.S.
1.85 ± 0.88 (17)	1.61 ± 1.16	−0.24 ± 1.09	N.S.
−1.08 ± 0.58 (17)	−1.14 ± 0.97	−0.07 ± 1.02	N.S.
−0.86 ± 0.79 (17)	−0.89 ± 0.33	−0.03 ± 0.9	N.S.
2.0 ± 0.9 (17)	1.65 ± 1.25	−0.3 ± 1.11	N.S.

and the concentration of plasma potassium and the increase in the amplitude of the T wave seen in acidosis[2, 23] is ascribed to hyperkalemia. In the present experiments there is no increase in the concentration of venous potassium. It is also reported that respiratory acidosis does not produce ECG alteration in dogs. Some cases of metabolic acidosis without hyperkalemia mentioned by Roberts and Magida are accompanied by a decrease in the concentration of plasma Na.

Eliakin and associates noticed bradycardia accompanied by a lowering of the voltage of the P wave and later that of the T wave in dogs upon injection of a 20 per cent solution of sodium chloride. This is as expected exactly the opposite of the result of the present experiments. Although an increase in the voltage of the P wave is not seen in myocardial hypoxia a low coronary blood flow cannot be excluded as a significant factor in the present experiments. Whether the ECG changes are related to a low cellular osmolarity or a decreased concentration of extracellular Na is not clarified by the present experiments.

The effects on oxygen consumption are similar to the findings of Harrop and associates[1] and DeLangen. Absence of a decrease in the oxygen saturation of arterial blood excludes a ventilation defect as a possible cause of the lowered uptake of oxygen. However, a low supply of blood to the tissues cannot be excluded as an important factor. Haddy and Fleishman found high peripheral resistance in acute salt depletion. Smith and Crowell found a decreased oxygen consumption in animals with low blood pressure and volume and high hematocrit in the absence of hyponatremia. The same mechanisms might account for the decreased oxygen consumption in acute salt depletion.

Summary

Acute salt depletion was produced in dogs by the intraperitoneal injection of 5 per cent glucose solution. Concentrations of serum sodium and potassium as well as hematocrit, blood pressure, oxygen consumption, and blood oxygen saturation were determined and electrocardiograms were recorded. The alterations are compared with those in a group of control

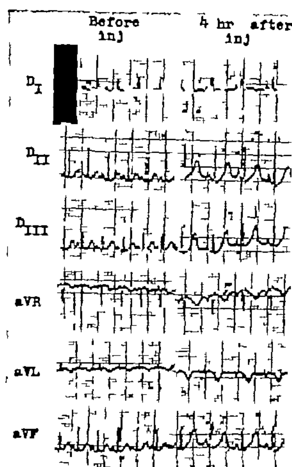


Fig. 1 Dog No. 25 ECG before and 4 hours after intraperitoneal injection of 5 per cent glucose solution.

animals that received Tyrode solution in the same way. A statistically significant increase in the amplitudes of the P and T waves and a decrease in oxygen consumption were observed. Their possible causes are discussed.

I wish to express my indebtedness to Prof. F. J. Haddy for critically reviewing the paper and to Prof. C. F. Calry for his valuable help in the preparation of this manuscript. Technical assistance by Miss F. Yamouti and Miss M. H. Zamani is gratefully acknowledged.

REFERENCES

1. Abrams, W. B. and Harris, T. N. The effect of cortisone on the electrocardiogram of normal rabbits, Am. Heart J 42:876, 1951
2. Abrams, W. B., Lewis, D. W., and Bellet, S. The effect of acidosis and alkalosis on the plasma potassium concentration and the electrocardiogram of normal and potassium depleted dogs, Am. J. M. Sc. 222:506, 1951
3. Altschule, M. D. and Sulzbach, W. M. Tolerance of the human heart to acidosis. Reversible changes in RS-T interval during severe acidosis caused by administration of carbon dioxide. Am. Heart J 33:458, 1947
4. Borst, J. G. G., DeVries, L. A., van Leeuwen, A. M., den Ottolander, G. J. H., and Cejka, V. The maintenance of circulatory stability at the expense of volume and electrolyte stability. Clin. Chim. Acta 5:887, 1960.
5. Darrow, D. C., and Yannet, H. The changes in distribution of body water accompanying increase and decrease in extracellular electrolytes, J. Clin. Invest. 14:266, 1935
6. DeLangen, C. D. Basal metabolism and sodium chloride, Acta Med. Scandinav. 150:257, 1954
7. Eliakim, M., Rosenberg, S. Z., and Braun, K. Electrocardiographic changes following the administration of hypertonic saline to dogs, Am. Heart J 58:97, 1959
8. Haddy, F. J. and Fleishman, M. Effect of acute salt depletion upon small and large blood vessels, Circulation 20:707, 1959
9. Hall, C. E., Dieren, H. W. and Hall, O.: Electrocardiographic abnormalities in desoxycorticosterone treated rabbits, Am. J. Physiol 176:130, 1954
10. Hall, C. E., Dieren, H. W. and Hall, O. Electrocardiographic abnormalities induced by corticoids. Potentiation by NaCl and reversal by KCl. Am. J. Physiol. 183:550, 1955
11. Harrop, G. A., Weinstein, A., Soffer, L. J. and Trescher, J. H. Studies on the suprarenal cortex. II. Metabolism, circulation and blood concentration during suprarenal insufficiency in the dog, J. Exper. Med. 58:1, 1933.
12. Henderson, R. F., Meroney, W. H. and Pearson, C. M. The electrocardiographic effects of alterations in concentration of plasma chemicals, Am. Heart J 50:188, 1955
13. Lubschez, R., and Magida, M. G. Electrocardiographic effects of cortisone and related compounds on the dog, Circulation Res. 2:123, 1954
14. Magida, M. G., and Roberts, K. E. Electrocardiographic alterations produced by an increase in plasma pH, bicarbonate and sodium as compared with those seen with decrease in potassium, Circulation Res. 1:214, 1953
15. Martin, H. E., and Wertman, M.: Electrolyte changes and the electrocardiogram in diabetic acidosis, Am. Heart J 34:646, 1947
16. Reynolds, T. B., Martin, H. E., and Homann, R. E. Serum electrolytes and the electrocardiogram, Am. Heart J 42:671, 1951
17. Roberts, K. E.: Effects of cortisone on electrocardiographic changes in adrenal insufficiency Proc. Soc. Exper. Biol. & Med. 79:32, 1952.
18. Roberts, K. E., and Magida, M. G. Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those produced by an increase in potassium, Circulation Res. 1:206, 1953.
19. Smith, E. E., and Crowell, J. W. Effect of hemorrhagic hypotension on oxygen consumption of dog, Am. J. Physiol. 207:647, 1964

Certain immunologic substances in the serum of patients with myocardial infarction and other cardiovascular diseases

Vernon N. Dodson, M.D.
*Park W. Willis III, M.D.**
*Lucas deVries, M.S.****
*Mary E. Clifford, M.D.*****
Ann Arbor, Mich.

Anti-heart antibodies have been detected by different immunologic methods in the serum of patients with various heart diseases, especially that of rheumatic origin.[1-4] The prevalence of these serum antibodies in patients with nonrheumatic heart disease has been relatively low.[5-8] Thus, the adjunctive use of immunologic methods for the clinical detection of heart disease appeared to be of limited value unless the sensitivity and yield of significant positives could be increased. This paper reports further studies on anti-heart serum factors which increase the diagnostic potential of such blood tests in patients with heart disease, especially myocardial infarction.

Methods and materials

Samples of serum were taken from patients with myocardial infarction. Serum from normal people and hospital patients with various diseases was also studied. In this study, a patient was considered to have a myocardial infarction if the electrocardiogram (ECG) showed typical changes of transmural infarction or if atypical changes were accompanied by an elevated serum glutamic oxaloacetic transaminase activity (SGOT). The antigens used in this study were prepared from human tissues which were histologically normal, obtained at postmortem within 6 hours of death from individuals with type O blood whose clinical course and postmortem examination revealed no evidence of cancer or infection. A modification of the Boyden tanned red blood cell hemagglutination tests was employed to detect anti-organ antibodies in the serum. Type O human erythrocytes were coated with a 1:1000 gram volume concentration of tissue antigen extract prepared in the following way. One gram of freshly washed tissue was homogenized in 10 ml. of phosphate-buffered normal saline, pH 6.4, for

From the Department of Internal Medicine, School of Medicine, Department of Industrial Health, School of Public Health, and the Institute of Industrial Health, University of Michigan, Ann Arbor, Mich.
This investigation was supported in part by a research grant from the Michigan Heart Association.
Received for publication April 12, 196[illegible].
*Associate Professor of Internal Medicine and of Industrial Health, and Research Associate, Institute of Industrial Health. Address: School of Public Health, University of Michigan, Ann Arbor, Mich., 48104.
**Professor of Internal Medicine.
***Graduate Student, Department of Epidemiology, School of Public Health.
****Assistant Professor, Internal Medicine.

2 minutes at 4 C using a Virtis homogenizer The homogenate was allowed to extract for 15 minutes at 4 C and then was centrifuged at 1 500 r p m for 10 minutes. The supernatant was diluted 1 100 with the buffered saline All extracts were prepared fresh and used within 90 minutes All runs contained the following controls a positive serum of known titer a negative serum and a typical checker board of cross reactions between all reactants. If the test serum did not hemagglutinate heart-extract sensitized tanned erythrocytes then a test for the presence of inhibitors was performed by adding a constant volume of anti heart positive serum to each tube of the negative test serum and the negative control serum series so that the tubes of the negative control series became positive. The tubes were shaken the cells resuspended and the test was read after 2 hours. If inhibitors were present, the tubes containing higher concentrations of test serum suppressed hemagglutination whereas those containing lower concentrations did not The titer of the inhibitor was taken as the dilution of the last tube in which hemagglutination was suppressed Some of the sera which gave negative results on direct hemagglutination were incubated with positive anti heart antiserum or with heart-extract-sensitized tanned red blood cells prior to repeating the test, in order to ascertain whether the site of action of the inhibition was with antibodies in the antiserum or with antigen on the erythrocytes or at both of these locations. Cross reactions with other organ extracts were studied with hemagglutination and hemagglutination inhibition methods.

Results

Table I presents the results of direct and inhibition hemagglutination tests performed on the serum of normal people and on that of patients with myocardial infarction The infarctions had occurred 9 days to 15 years earlier The difference in the prevalence of positive hemagglutination tests between the group with myocardial infarction and the normal group is significant for both direct ($p < 0.05$) and inhibition ($0.025 > p > 0.01$) testing

Table II presents the data on serum *hemagglutination tests in patients with* various diseases. Direct hemagglutination occurred in cases of heart disease Positive inhibition reactions occurred in patients with diseases which usually involve blood vessels, e.g lupus erythematosus syphilitic aortitis and pulmonary embolism

Table III presents the results of tests for the presence of anti heart hemagglutination inhibitors in sera which were negative for anti heart antibodies by direct hemagglutination When the test sera were preincubated with the antigen-coated cells the results were identical to those obtained with the initial inhibition test. Inhibition occurred with the serum from one patient in the myocardial infarction group (No 5) and with that from the three persons in the normal group (Nos. 8 9 and 10) regardless of whether preincubation was with antigen-coated cells or anti heart antiserum All four had titers of 1 128 or 1.256. Serum from Patients Nos. 2 4 and inhibited only after incubation with anti heart antiserum

Table IV lists the hemagglutination test results with the intervals since the oldest and most recent infarctions.

Table I Results of serum anti-human heart hemagglutination tests in normal people and patients with myocardial infarction

Patient groups	*Direct hemagglutination*			*Inhibition hemagglutination*		
	Positive	*Negative*	*Total*	*Positive*	*Negative*	*Total*
Myocardial infarction	8	15	23	7	6	15
Normal	3	47	50	3	20	23

*Numbers indicate the number of people in each category

*Table II Results of serum anti-heart hemagglutination tests in patients with various diseases**

Disease	Direct hemagglutination			Inhibition hemagglutination		
	Positive	Negative	Total	Positive	Negative	Total
Cardiomyopathy	2	3	5	1		3
Miscellaneous						
Rheumatoid arthritis	1	0	1			
Rheumatic heart disease	4	1	5	0	1	1
Lupus erythematosus (SLE)	0	1	1	1	0	1
Syphilitic aortitis	0	1	1	1	0	1
Pulmonary embolism	0	1	1	1	0	1
Pleurisy	0	1	1	1	0	1
Electrical shock	0	1	1	0	1	1
Cancer of pancreas	0	1	1	0	1	1
Osteoarthritis	0	1	1	0	1	1

*Numbers indicate the number of people in each category

Table III Results of anti-heart hemagglutination inhibition tests

Patient number	Direct hemagglutination	Initial inhibition test	Pre-incubation with	
			Heart antigen coated red blood cell	Anti-heart antiserum
Myocardial infarction				
1	−	+	+	−
3	−	+	+	−
5	−	+	+	+
6	−	+	+	−
2	−	−	−	+
4	−	−	−	+
7	−	−	−	+
Normal				
8	−	+	+	+
9	−	+	+	+
10	−	+	+	+

Discussion

The sera of 29 per cent of the patients with myocardial infarction gave positive anti-heart hemagglutination tests, as compared to 6 per cent in the normal group ($p < 0.005$). This low frequency of positive tests in normal individuals has been reported. The prevalence of positive tests in the group with myocardial infarction compares favorably with the experience of others employing similar methods and precipitin procedures[11] but is less than that observed with immunofluorescent techniques. Four of 5 patients with inactive rheumatic heart disease had positive anti-heart hemagglutination test. This is similar to the frequency (92 per cent) reported by Zabriskie. Hess and Fink found 63 per cent positive results in patients with active rheumatic

Table IV. Intervals between anti-heart hemagglutination tests and myocardial infarction

Interval since myocardial infarction		Direct hemagglutination (reciprocal of titer)	Inhibition hemagglutination (reciprocal of titer)
First	*Last or only*		
10 yr	?	256	
	14 days	32	
15	22 mo.	64	
	18 day	4	
	9 days	256	
	6 mo.	4	
4 yr	21 days	128	
3 yr	?	128	
8 mo	6 days	Negative	128
?	8 y	Negative	128
?	7 days	Negative	1,028
10 yr	47 days	Negative	0
	11 days	Negative	0
	2 mo.	Negative	128
	45 days	Negative	0
	?	Negative	0

? = Exact date of infarction not known.

heart disease, but only 16 per cent in patients in whom the disease was in the inactive stage. Occasional reports of tests of the serum of individuals with cardiomyopathy have been included in papers on anti-heart serum factors.[1] Two of 5 such patients in this study had anti-heart antibodies.

These findings indicate a firm relationship between anti-heart serum hemagglutinins and structural heart disease, with the former being more likely an effect than a cause of the heart disease except, perhaps, in the case of acute rheumatic fever.[7,8] There appears to be no clear relationship to a single pathologic change in the heart, since anti-heart hemagglutination reactions occurred in patients whose hearts were involved by acute or chronic inflammatory, degenerative, or necrotic processes, a situation also reported by others.[2,11,17] It would seem that these patients are responding to a number of heart antigens by forming immunoglobulins that range from relatively nonspecific to cross-reacting or highly specific.[11,13,21,24] Serum from normal individuals and from patients with vascular or other cardiac diseases did not often give the positive anti-heart hemagglutination test results commonly encountered with serum from patients with myocardial infarction, rheumatic heart disease, or cardiomyopathy. There was no association between the presence or titer of anti-heart hemagglutinins and the number of infarctions or the interval since infarction. In rheumatic heart disease, cross-reacting antistreptococcal wall antibodies as well as anti-heart factors could be responsible for the positive tests observed. Anti-heart serum factors have been reported in lupus erythematosus and syphilis,[8,11,13] but were not detected in this study. The serum in one case of inactive rheumatoid arthritis produced hemagglutination at a titer of 1:16.

Anti-heart hemagglutination inhibitors were more frequently encountered in the serum of patients with myocardial infarction than in that of normal subjects (Table I), but were observed in the serum of patients with cardiomyopathy, lupus erythematosus, syphilitic aortitis, pulmonary embolism, and pleurisy. Except for the case of pleurisy, they were not found in the absence of cardiac or vascular disease (Table II).

Three types of anti-heart hemagglutination

nation inhibition are observed at the antigen site at the antiserum site, or at both sites. Except for the serum of one patient with myocardial infarction, dual inhibition occurred only in the serum from 3 normal subjects. Anti-heart inhibitors are relatively uncommon in normal individuals in contrast to patients with myocardial infarction. They are also observed in persons with other diseases in which there is cardiac or vascular involvement (cardiomyopathy lupus erythematosus, syphilitic aortitis, and pulmonary embolism). Inhibition was not present in *the one case of inactive rheumatic heart* disease studied.

It seems therefore that chronic inflammatory mechanisms involving the cardiovascular system are frequently associated with solitary anti-heart hemagglutination inhibitors acting at either the antigen or antiserum site. Sera exhibiting dual inhibition are less specific and were found in normal subjects and in one patient with myocardial infarction. Inhibitors in serum were observed as early as 6 days and as late as 2 months after myocardial infarction (Table IV). Titers ranged from 1 128 to 1 1028 and were present in persons with one infarction as well as in those with several infarctions. There were no apparent correlations between the titers of inhibitors, the time since infarction or the number of infarctions.

The immunologic significance of these findings is difficult to assess. The inhibition observed against the heart antigens could be explained by the presence of incomplete anti-heart antibodies or cross-reacting immunoglobulins, but is more likely due to anti-heart immunoglobulins of the G or 7s type.[22,26] Inhibition occurring at the antiserum site could be the result of circulating heart antigens other tissue antigens possessing similar determinants[22] or anti gammaglobulins (e.g. serum normal agglutinators, rheumatoid agglutinators, Milgrom factors, etc.[28]) The nonspecific dual inhibition could be explained by the presence of several of the latter factors, especially those immunoglobulins acting against antigen antibody complexes, gammaglobulin aggregates, or proteins with semi-available determinants. Other investigators have presented evidence to suggest that damaged tissue itself releases nonspecific immunoglobulins which persist for weeks.[4,32]

Although the reason for the presence of the anti heart inhibitors is not apparent they are found in the serum of patients with heart disease and may prove to have diagnostic usefulness.

Summary

Serum anti heart hemagglutinins occurred in 29 per cent of patients with myocardial infarction as compared to 6 per cent of normal control subjects, had a high prevalence in patients with rheumatic heart disease, occurred in 2 of 5 with a cardiomyopathy and had a very low frequency in individuals who had non cardiac diseases with or without a vascular component.

Serum inhibitors of anti-heart hemagglutinations were found in one half of the patients with myocardial infarction and in those having diseases with vascular involvement, e.g. lupus erythematosus pulmonary embolism and syphilitic aortitis. The inhibitors found associated with cardiovascular diseases inhibit at either the antigen or antiserum site during the hemagglutination test, whereas the normal sera which display inhibition do so at both sites, suggesting a lack of anti-heart specificity. From these data it appears that with the sequential use of both the anti-heart hemagglutination technique and the inhibition test, positive results can be obtained in over one half of the patients with myocardial infarction.

As diagnostic adjuncts, these tests still offer only limited assistance in the clinical detection of cardiovascular diseases. A positive anti heart hemagglutination inhibition test alone appears to be related to less specific vascular damage.

REFERENCES

1. Gery, L., Davies, A. M. and Ehrenfeld, E. N. Heart-specific autoantibodies, Lancet 1:471, 1960.
2. Davies, A. M. and Gery, I. The role of autoantibodies in heart disease, Am. Heart J. 60:669, 1960.
3. Zablocki, B. Szydlowski, S. Kotelko, K., Seykler L., Kandel, S. and Odlanicki-Poczobut, A. Search for antibodies to heart antigens in the sera of patients with rheumatic fever

and rheumatoid arthritis, Bull. Acad. Pol Sc 12:251 1964

4 W gner \ Za zal \ Kasalova, D Mal \ Merl \ and Prokop, J Immunology of toxemia of pregnancy I Findings of organ-specific ntibodies Experientia 15:24 1959

5 Ehrenfeld, E \ Gery I and Davies, A. M Specific tibodies in heart disease Lancet 1 1138 1961

6. Hess E \ and Fink, C W Heart muscle ant bodies heumatic fever and other diseases, J Clin Invest. 43:886, 1964

7 Yamada, S Immunofluorescent studies on tumyocardial antibodies in rheumatic fever and other diseases, J J p. Rheum. Amn 8 193 1964

8 Kaplan M H The concept of utoantibodies in rheumatic fever and in the post-commisurotom tate Ann New York Acad Sc. 86:974 1960

9 Bowden, S J The adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by antiprotein sera, J Exper Med 93 107 1951

10. Robinson, J and Brigden, W Immunologic studies in the postcardiotomy yndrome Brit M J 2 706 1963

11. Djanian, A \ Beutner E H and Witebsky E Tanned-cell hemagglutination test for detection of antibodies in sera of patients th myasthenia gravis, J Lab & Clin. Med. 63:60, 1964

12. F tenkov \ \ Precipitin reaction with myocardial ntigens in m ocardial infarction and other diseases, (Russian) Terap Arkh 33 11 1961

13. * der Geld H Anti-heart antibodies I the postpericardiotomy and the postmyocardial-infarction yndromes, Lancet, 2:617 1964

14. Ziffer A M and Klotz, S. D Post myocardial infarction ndrome, A n. Allergy 21:698, 1963

15 Kaplan, M H and Meyeserian, M An immunological cross-reaction between Group A treptococcal cells and human heart tissue, Lancet 1 706, 1962

16. Kaplan, M H Bolande, R., Rakita, L and Blair J Presence of bound imm noglobulins and complement in the myocardium in acut rheumatic fever New England J Med. 271:637 1964

17 D vries, A. M Laufer A nd Gery I Organ specificity of the heart. III Circulating antibodies and immunopathological lesions in experimental animals, Arch. Path. 78:369 1964

18 Kaplan, M H Meyeserian, M nd Kushner I Immunologic studies of heart tissue IV Serologic eactions with human heart tissue as revealed by immunofluorescent methods Isoimmune Wassermann, and autoimm ne reactions, J Exper Med. 113 17 1961

19 Szent-Gyorgyi, A. G and Holtzer H Fixation of muscle proteins th antibodies, Biochim Biophys. Acta 41 14 1960

20 Kesztyus, L. Nikodemusz, S and Szilagy T Antigenic activity of myosin and actin, Nature 163 136 1949

21 Gery I Davies, A M and Lazarov E Immunity and immuno-tolerance t bovine heart ntigens in the t. Heterogeneity of the serologic esponse Immunology 7 182, 1964

2 Kabat, E \ and M er M M Experimental immunochemistr ed 2, Springfield, Ill 1961 Charles C Thomas, pp. 241 267

23 Rozental K. M nd Romanov A. F Incidence of autoantibodies in the blood of children with rheumatic fever (Russian) Vop Revm 4:3-8, 1964

24 Neff B J Ackermann W W Epstein, F H. and F ancis, T J Inhibition of vaccinial hemagglutinins b sera of patients with coronary heart disease and other chronic illnesses, Circulation Res. 10:836, 1962.

25 Kunkel H Ct Advances in immunology Vol IV New York, 1964 Academic Press pp. 351—396

26 Dodson, V N Friberg R. nd Ketch m, D Chemical, histologic and immunologic re sponses in rats to CCl by different outes f administration Proc Soc Exper Biol & Med 120:355 1965

27 Weir D M Immunological reactions after tissue damage Lancet 1 749 1964

Catecholamine secretion and sympathetic nervous responses to emotion in men with and without angina pectoris

P J Nestel M D
A Verghese M B B S B Sc D P M
R. R. H Lovell M.D
Victoria Australia

Myocardial ischemia which may become manifest clinically as angina pectoris, occurs whenever the energy requirements of the heart exceed the available supply of oxygen Emotion commonly induces angina pectoris in people with coronary heart disease and several lines of evidence suggest that this effect of emotion may be brought about by an increased secretion of the catecholamines epinephrine and norepinephrine. The concentrations of the urinary catecholamines rise during emotional stress, and a quantitative relationship has been demonstrated between the stress experienced by an individual and his urinary excretion of catecholamines. The infusion of norepinephrine into normal subjects leads to an increase in the extraction of oxygen by the heart and a fall in the oxygen saturation of coronary venous blood changes which characteristically occur during exercise in patients with coronary insufficiency It is well known that the infusion of norepinephrine into subjects with coronary heart disease may induce angina pectoris.

Several studies have attempted to differentiate subjects with coronary heart disease from healthy subjects by their response to procedures which stimulate the sympathetic nervous system Significantly higher levels of plasma free fatty acids, a sensitive index of catechol amin secretion have been reported in subjects with coronary heart disease than in normal men after smoking[1] and after a standard test in mental arithmetic. Men whose behavior pattern and serum lipid levels are thought to indicate a high incidence of coronary heart disease have been reported to excrete greater amounts of 3-methoxy-4-hydroxy mandelic acid (VMA) the major urinary metabolite of epinephrine and norepinephrine, than men in whom coronary disease is less frequent

A direct relationship between the secretion of catecholamines and the occurrence of angina pectoris has not however been demonstrated This paper reports the measurements of the three major catecholamine metabolites which appeared in urine—VMA normetanephrine and metanephrine —after a standardized mental stress test in subjects all of whom had

With the technical assistance of Judy Hammond and P Drew
From the Department of Medicine, University of Melbourne, and the Royal Melbourne Hospital, Victoria, Australia
Supported by a grant from the Life Insurance Research Fund of Australia and New Zealand
Received for publication April 21 1964.

*Normetanephrine and metanephrine are derived exclusively from norepinephrine and epinephrine, respectively VMA is derived from both catecholamines.

had myocardial infarctions and who were classified before the test as experiencing or not experiencing angina pectoris.

Experimental methods

Thirty two men who had sustained a myocardial infarction 6 to 18 months previously were selected for study. They were seen at frequent intervals at a special clinic and were familiar with such procedures as electrocardiography and venepuncture. It is also likely that a reasonable degree of trust had developed between subjects and investigators before the subjects were asked to take part in the study. The purpose of the experiment and the procedures were explained simply and were accepted without apprehension.

The subjects studied were from 106 patients admitted consecutively to the clinic in whom the frequency and character of chest pain was being investigated. The presence or absence of chest pain and its type were determined before the stress test by one of us who did not participate in the subsequent investigations and the classification of the patients with regard to pain was not known to the person conducting the stress test. The subjects used in this study were classified into 4 categories of pain.

A. Angina pectoris. These were subjects who (1) had experienced discomfort or pain in the chest since leaving hospital and (2) recognized only one type of chest pain. The pain had to fulfill the strict criteria proposed by Rose for the definition of angina pectoris.

B. Left chest pain. These were subjects who had also experienced chest pain since leaving hospital but whose pain was not related to effort as defined by Rose.[8] The pain was felt over the anterior part of the left side of the chest.

C. Other chest pains. These were subjects with any chest pains or discomforts that did not fulfill the criteria for Group A or Group B.

D. No chest pain. These were subjects who in reply to a standard question denied having had chest pain since leaving hospital.

The final classification was based on the questionnaire, together with a clinical appraisal of the patient's status during the 6 months preceding the study. Thirty four men who were less than 65 years of age and who were born in Australia or Great Britain were then selected consecutively from the clinic for study, the numbers in each group being kept similar. Thirty two of 34 men agreed to take part.

The subjects arrived in the laboratory in the early morning after having fasted overnight. Smoking was prohibited. They drank water as desired, rested in a quiet room and were asked to empty their bladders at hourly intervals. It was found that the urinary VMA levels did not reach a base line until the second or third hour after arrival and only these later samples were assayed. The subjects were then moved to another room where a series of mildly stressful procedures were carried out intermittently during the next 2 hours. The procedure during each study was uniform and great care was taken to avoid unnecessary noise or movement.

The procedure was as follows. The subject reclined on a couch in a room in which the temperature was kept constant at 72 to 74 F. He was told that the test consisted of measurements of normal body functions before and during a mildly stressful situation. A strain-gauge belt was placed across the chest to measure the respiratory rate and the heart rate was monitored with an ECG. Electrodes were placed on the palms of the hand to measure skin conductance and across the frontalis, left pectoralis major and left trapezius muscles for electromyography. After the electrodes had been placed the pre-stress measurements, including heart rate and respiratory rate were taken over a period of 10 minutes on a Type R Offner polygraph. The subject was then asked to solve a series of puzzles of increasing difficulty (the progressive matrices of Raven[7]). Since the subject could not move the pages of the book of progressive matrices were turned by a technician. This portion of the study took 20 minutes, during which time measurements including those of heart rate and respiration rate were recorded continuously. A sample of blood for determination of plasma free fatty acids was taken 7 minutes after the completion of the progressive matrices. The electrodes

were then removed and the subject's height and skinfold thickness were measured. He then completed a questionnaire (Taylor's manifest anxiety scale[1]) which consists of 50 questions. An estimate of the subject's pain threshold was then made by applying increasing intensities of radiant heat to the blackened surface of his forehead using a Hardy Wolff thermal stimulator. This final portion of the study occupied 20 minutes. The subject then returned to the room in which he had been previously. This portion of the study was carried out by only one of us and the one technician.

Urinary VMA was measured by the method of Pisano, Crout and Abraham[12] and the measurements were expressed as micrograms (μg) of VMA per milligram (mg) of creatinine.[13] The VMA excretion was related to creatinine excretion in order to take into account minor variations in the glomerular filtration rate (GFR). There were however no appreciable differences in urinary creatinine excretion during the studies. Urinary normetanephrine and metanephrine were measured by a minor modification of the method of Taniguchi and associates.[14] Plasma free fatty acids (FFA) were measured by Dole's method.[15]

This paper presents the changes in catecholamine metabolites produced by the stress. The results of some of the biological and psychological measurements are also reported and discussed but these aspects will be published in detail elsewhere.

Results

There were 10 men in Group A (angina pectoris) 8 men in Group B (left chest pain) 6 men in Group C (other chest pains) and 8 men in Group D (no chest pain). The mean ages body weights, and weight to height ratios of the respective groups did not differ significantly. The mean age for the whole group was 53 years.

Urinary catecholamine metabolites. The mean basal pre-stress concentrations and the maximum post-stress changes in urinary VMA excretion are shown in Table I. There was a rise in VMA excretion in every study and the peak post-stress VMA level was found in most subjects during the second hour after the stress test. The differences between the mean basal pre-stress VMA concentrations did not differ significantly among the four groups. However significant differences were found in the mean post-stress concentrations (Table II).

The mean increment in the group with

Table I. *Maximum changes in urinary VMA after stress**

Maximum urinary VMA change (μg VMA per mg of creatinine)			
Angina pectoris Group A (10)	*Left chest pain Group B (8)*	*Other chest pains Group C (6)*	*No chest pain Group D (8)*
1 0	0 5	0 2	0 1
1 6	1 0	0 8	0 3
1 8	1 4	0 8	0 6
2 4	2 0	1 1	0 7
2 5	2 2	1 7	0 7
3 0	2 6	2 3	1 0
3 1	2 8		1 1
3 4	3 0		3 2
4 0			
5 1			
Mean ± SD 2 79 ± 1 20	1 93 ± 0 87	1 15 ± 0 74	1 01 ± 0 97

*Differences between the basal pre-stress and peak post-stress measurements.
The mean basal VMA concentrations for the Groups A, B, C, and D were 3.3, 3 7 3 7 and 3.3 μg per milligram of creatinine respectively (differences not significant).

Table II. Statistical analysis of difference between mean VMA increments

Comparison		p Value
Angina pectoris	Left chest pain	0.1–0.2
Angina pectoris	Other chest pains	<0.01
Angina pectoris	No chest pain	<0.01
Left chest pain	Other chest pains	.05–0.1
Left chest pain	No chest pain	<0.05
Other chest pains	No chest pain	0.7–0.8

angina was significantly greater than that in the groups with no pain and other chest pains. The mean increment in the group with left chest pain was intermediate between that in the group with angina and that in the groups with no pain and other chest pains. Subjects with left chest pain excreted significantly more VMA after the stress than did subjects without chest pain. Subjects without chest pain and those with other chest pains showed similar post-stress increments.

Measurements of urinary normetanephrine and metanephrine were limited to 7 subjects in Group A (angina) and 7 subjects in Group D (no chest pain). Results are shown in Table III. All subjects excreted more normetanephrine than metanephrine in the basal state. The two groups did not differ significantly during the prestress period. Peak excretion of metanephrine occurred in most subjects during the first hour after the completion of the stress, whereas peak excretion of normetanephrine was generally found during the second hour. The maximum post-stress increments were substantially greater for normetanephrine than for metanephrine for subjects in Group A. The mean increment in normetanephrine concentration was significantly greater in Group A than in Group D ($p = < 0.01$). On the other hand, the mean increments in metanephrine concentration were similar in the two groups.

A significant positive correlation was found between the increments in normetanephrine and VMA excretion ($p = < 0.01$) but not between the increments in metanephrine and VMA.

Plasma FFA. The mean plasma FFA concentrations at 7 minutes after the completion of the progressive matrices were determined in 23 subjects. The mean concentrations for Group A, Groups B and C combined, and Group D were 615, 600, and 540 μM per liter, respectively, and the differences between the groups were not significant.

Since mobilization of FFA from adipose tissue into plasma depends to a large extent on adrenergic activity, the plasma levels of FFA were related to the increments in urinary VMA excretion. A significant relationship was demonstrated ($p = < 0.02$).

Other biologic measurements. The changes in heart rate and respiration rate were calculated as the differences between the means of six readings taken at fixed intervals before and of six readings taken at similar intervals immediately after beginning the progressive matrices. The changes in blood pressure represent the differences between the means of three readings taken 10 minutes before starting

Table III. Mean basal concentrations and mean maximum increments in urinary normetanephrine and metanephrine after stress in 7 subjects in Group A and in 7 subjects in Group D

Group	Normetanephrine (μg per mg. of creatinine)		Metanephrine (μg per mg. of creatinine)	
	Basal level	Maximum increment	Basal level	Maximum increment
A. Angina	0.053	0.097	0.030	0.021
D. No chest pain	0.049	0.02[illegible]	0.026	0.021

Table IV Mean changes in heart rate respiratory rate and blood pressure†

	Angina pectoris (12)‡	*Left chest pain (10)*	*Other chest pain (8)*	*No chest pain (12)*
Heart rat (per minut)	8§	5 3	2 8§	4 6
Respiratory rate (per min t)	3 2	2 2	1 9	1 6
Blood pressure (mm. Hg)	8 6	10 2	8 9	9 0

*Difference between means of six 1-minute readings before and after commencing the progressive matrices.
†Difference between three readings before beginning, and three readings shortly before finishing, the progressive matrices.
‡Including additional studies in which urinary VMA was not measured.
§Difference between means for angina pectoris and other chest pains significant at 5 per cent level

and three readings taken shortly before finishing the progressive matrices.

Measurements of heart rate respiratory rate and blood pressure were carried out in a slightly larger group as shown in Table IV The mean change in heart rate was greatest for the group with angina pectoris, but a significant difference was found only between the subjects with angina pectoris and those with other chest pains.

Since heart rate is directly influenced by the sympathetic nervous system a relationship was sought between the changes in heart rate and VMA excretion. A significant positive regression was found (p = < 0 05)

The mean changes in respiratory rate and in the blood pressure did not differ significantly among the four groups (Table IV)

Discussion

These results demonstrate a significant degree of variabil ty in the response to stress among subjects who have had a myocardial infarction It has been previously observed that subjects with coronary heart disease as a group show a greater adrenergic response than do healthy subjects to procedures which stimulate the sympathetic nervous system The present study shows that subjects all of whom have had a myocardial infarction can be further differentiated according to their subsequent experience of chest pain Those who subsequently suffer from angina pectoris clearly show a greater sympathetic response than do those who have no further chest pain This conclusion is based upon the significantly greater rise in urinary VMA and normetanephrine in subjects with angina pectoris than in those who are free of chest pain (Tables I III)

However this increased sympathetic responsiveness is not found only after myocardial infarction in those who experience angina pectoris Patients who do not have angina but who experience pain in the left side of the chest which is not brought on by effort also excrete more VMA in response to a standard stress than do patients who deny experiencing pain after their infarction. On the other hand the responsiveness of the subjects with the heterogeneous other chest pains, which generally appeared to arise in the gastrointestinal tract or shoulder girdle, was similar to that of the group with no chest pain. It seems therefore that increased sympathetic responsiveness is not simply a nonspecific consequence of repeated experience of pain in the chest after myocardial infarction.

The cause of the left chest pain in these patients is not at present known It has many of the features of the pain of Da Costa s syndrome but to liken it to this does not explain it Studies in progress (unpublished observations by Verghese) suggest that patients in the group with left chest pain differ in personality from those in the other groups particul rl n having the highest scores for neuroticism as measured by the Eysenck personality inventory It is possible that their sympathetic responsiveness and neuroticism may be related It is thought unlikely that left chest pain in these patients is ischemic in

origin, although this possibility cannot be entirely ruled out.

The increments in urinary metanephrine were smaller than the increments in concentrations of normetanephrine in subjects with angina. Furthermore the mean changes in the urinary concentration of metanephrine after stress were similar in men with and without angina. Since metanephrine and normetanephrine are specific metabolites of epinephrine and norepinephrine, respectively, it follows that the men with angina secreted significantly more norepinephrine after stress than did the men without angina but similar amounts of epinephrine. Therefore it also seems to be likely that the greater rise in VMA excretion in subjects of Group A than in those of the other groups can be accounted for by the predominant increase in the secretion of norepinephrine. This is also reflected in the significant relationship which was found in this study between the increments in VMA and normetanephrine excretion. Such a relationship did not exist between the excretions of VMA and metanephrine. This distinction in predominance of secretion between norepinephrine and epinephrine after stress appears to depend to some extent on the quality of the emotional response to the stress.[7] Furthermore there is evidence that the biologic changes which are observed during stress that provokes mental effort can be reproduced more readily by the infusion of norepinephrine than epinephrine.[4]

The probable difference between the secretion of norepinephrine and the secretion of epinephrine found in this study is in accord with a preliminary note by Hames and associates who found that the 24-hour urinary excretion of norepinephrine but not that of epinephrine was significantly higher among men with coronary heart disease than among healthy men. Increased excretion of norepinephrine but not of epinephrine has also been described in heart failure.[22]

The differences in the measurements of other biologic functions among the four groups were not great (Table IV). The changes in heart rate and respiratory rate were a little greater in subjects with angina than in the others. Measurements of urinary catecholamines or their metabolites may either be a more sensitive index of emotional stress or reflect more accurately the stress experienced over a longer period of time.

Before the significance of these findings can be estimated other possible reasons for an increased sympathetic response need to be considered. Lean subjects differ from obese subjects in the magnitude of the rise in their plasma FFA after stress,[21] but there were no significant differences between our three groups with respect to body weight and weight to height ratio. Furthermore a relationship between VMA excretion and either of these indices of body fatness could not be demonstrated. It has been shown that subjects in heart failure secrete greater amounts of norepinephrine during exercise than do subjects without heart failure.[22] None of our subjects had been in heart failure and the mean cardiothoracic ratios estimated from recent radiographs did not differ significantly among the four groups.

The relatively high rate of VMA and normetanephrine excretion in men with angina pectoris is, therefore not related to their body weight or to the presence of heart failure but may be a manifestation of some personality trait.

These findings raise the question whether an excessive rise in catecholamine secretion may precipitate angina pectoris.

It has been suggested for a long time that increased sympathetic nervous discharges may lead to the development of angina pectoris. The evidence from the earlier literature has been reviewed by Raab.[23] Recently published studies appear to be consistent with this hypothesis. Horwitz and Sjoerdsma[24] and Gorlin[25] have observed rises in heart rate and in blood pressure shortly before an attack of angina pectoris. Nocturnal angina pectoris has also been found to be preceded in some subjects by a rise in heart rate and respiratory rate and these changes have been ascribed to dreaming. Measurements taken during spontaneous angina have demonstrated a rise in coronary vascular resistance which was associated with generalized vasoconstriction elsewhere in the body.[25]

Angina pectoris which is related to

smoking (and the inhalation of nicotine) is also probably related to an increased secretion of catecholamines. In subjects with coronary heart disease cigarette smoking leads to a substantial increase in cardiac work without a rise in coronary blood flow and these effects have been attributed to catecholamines.[17] Moreover when norepinephrine is infused intravenously there is an initial reduction in coronary blood flow[1] and studies on isolated canine hearts have demonstrated that norepinephrine constricts the coronary arteries[18] the secondary rise in the coronary blood flow which follows the infusion of norepinephrine into man is secondary to the rise in myocardial metabolism and the utilization of oxygen produced by the hormone.

Gregg and Sabiston[19] have defined this effect as that of a malignant vasodilator With true primary vasodilation an increase in myocardial utilization of oxygen is accompanied by an increase in flow so that the oxygen saturation of the coronary venous blood remains unaltered or even rises.[16] With norepinephrine, on the other hand a rise in oxygen extraction results in a fall in the oxygen content of coronary venous blood[1] and a rise in lactate a response which also characterizes subjects with coronary heart disease during exercise[1,21] during spontaneous angina[22] and in response to isoproterenol[23] Norepinephrine may therefore precipitate myocardial ischemia especially in subjects in whom the coronary perfusion pressure is impaired. Our findings of increased rates of secretion of catecholamines in response to stress in men with angina pectoris may therefore be relevant to the development of angina pectoris. In a recent study (unpublished observations by Nestel and associates) we have found a significant correlation between the postexercise electrocardiographic changes and the excretion of catecholamines in subjects with coronary artery disease

Summary

Several indices of sympathetic nervous activity in response to emotion were measured in four groups of subjects who had had a myocardial infarction Group A men with angina pectoris Groups B and C men with left chest pain and other chest pains thought not to be angina pectoris and Group D men without chest pain

The concentrations of urinary VMA (3-methoxy-4-hydroxy mandelic acid) normetanephrine, and metanephrine the major metabolites of epinephrine and norepinephrine were measured before and after a standardized mental stress test.

The mean excretion of urinary VMA was significantly greater after the test in Group A than in either Group C or Group D Subjects in Group B excreted significantly more VMA than did those in Group D The mean excretion of normetanephrine (but not of metanephrine) was significantly higher in Group A than in Group D this was not measured in subjects in Group B or Group C These findings suggest that the rise in catecholamine metabolites can be largely accounted for by an increase in the secretion of norepinephrine.

The mean increments in heart rate respiratory rate and plasma free fatty acids were also highest in group A but the differences did not reach statistical significance

These findings demonstrate that although subjects with angina pectoris show a heightened sympathetic nervous response to mental stress, a heightened response is also found among men with coronary heart disease whose pain is localized to the left side of the chest and is not typically anginal

We gratefully acknowledge the advice received from Professor B. Davies and Dr R. Mowbray and the use of the facilities of the Department of Psychiatry University of Melbourne We also thank the physicians of the Royal Melbourne Hospital for allowing us to study their patients.

REFERENCES

1. Elmadjian, F Hope J M and Lamson, E. T Excretion of epinephrine and norepinephrine in various emotional states, J Clin Endocrinol 1 :608, 1957
2. Levi, L. The urinary output of adrenaline and noradrenaline during experimentally induced emotional stress in clinically different groups Acta psychotherap 11:218 1963
3. Yurchak, P M Rolett, E. L Cohen L. S and Gorlin, R. Effects of norepinephrine on the coronary circulation in man, Circulation 30 180, 1964.
4. Wegman, R J Levine, H J Messer J V Neill, W A., Krasnow N and Gorlin, R.

Coronary insufficiency in ma Physiologic and electrocardiographic correlation, Am. J Cardiol 9:439 1962

5 Kershbaum A Bellet S Capla R F and Felnberg L J Effect of cigarette smoking on f ee f tt acids in patie ts w th healed myocardial infarction Am. J Cardiol. 10:204 1962

6. Pennick S. B Greater non-esterified f tty acid response t moderate challenge in men th coronary heart disease, Clin. Res 10:402, 1962

7 B ers, S O Friedma M Rosenman, R H nd F eed, S C Excretion of 3-methoxy-4-h drox mandelic acid in men ith beha iour pattern associated with high incidence of coronary artery disease, Fed. P oc 21 (Suppl 11) 99 1962

8. Verghese A nd Lovell R R H The classification of hest pains fter m ocardial infarc tion Brit M J I press

9 Rose C A The diagnosis of ischaemic heart pain and intermittent laudication in field surveys, B ll World Health Org nization 27:645 1962

10 Ra en J C Progressive matrices, London, 1938 H K Lew s & Co.

11 T lor J A A personality scale of manifest anxiety J Abnorm. & Social Psychol 48:285 1953

12 Pisano, J J Crout J R and Abraham D Determination of 3-methoxy-4-h drox mandelic acid in urine Clin Chim Act 7:285 1962

13 King E J nd Wooton I D P Micro-anal sis in medical biochemistry ed 3 London 1956 J & A Churchill, Ltd.

14 Taniguchi, K Kakimot Y nd Armstrong M D Qua t tat e determination of metanephrine and normetanephrine in urine, J Lab & Cl Med 64:469 1964.

15 Dole V P A relation between non-esterified fatty acid in plasma and the metabolism of glucose J Clin I est. 35 150 1956.

16 Lov ll, R R H Some sequels to myocardial infarction and their treatment Brit M J 2:463 1964.

17 Von E ler U S Qua t tation of stress by catecholamine anal sis, Clin Pharmacol Therap. 5:398 1964

18 Kezywanek H. J Raab, W nd Bohle E Einfluss des sympathikoadrenalen Sy tems uf Herz Kreislauf Regulation und on erstert Fettsäuren des Blutserums, Deutsche med Wchnschr 91 193 1966.

19 Hames, C. G., Lightman, M A nd M Donough, J T Postexercise plasma nd urinary norepinephrine and epinephrine levels among high social class nd low social class males and subjects with nonacut coronary heart disease in Evans Cou ty Georgia, Circulation 32 (Suppl. II) 103 1965

20 Chidsey C A Braun ld, E. and Morrow A Catecholamine excretion and cardiac stores of norepinephrine congestive heart f ilure Am J Med. 39:442, 1965

21 Klei R F T over W G Back, K. W Hood, T C and Bogdonoff M D Experimental tress and f t mobilization i les and obese subjects Metabolism 14 17 1965

22. Chidsey C. A Harrison, D C and Bra ald E Augmentation of plasma norepinephrine response t exercise patie ts ith congestive heart failure New England J Med. 26 :650 1962.

23 Raab, W The sympathogenic biochemical trigger mecha ism of angina pectoris, Am J Cardiol 9:576 1962

24 Horw tz, D and Sjoerdsma, A. Some inter relationships bet een elev tion of blood pressure nd ngina pectoris, Hypertension, Vol. XIII p 39 New York, 1965 American Heart Association.

25 Gorli R P thophy iology of cardiac pain, Circulation 32 138, 1965

26. Nowlin J B T over W G Collins, W S Silverman, G Nichols, C R M I tosh, H D Estes, E H and Bogdonoff M D The association of nocturnal angina pectoris th dreaming A n. Int. Med. 63 1040, 1965

7 Regan, T J Hellems H K. and Bing R J Effect of cigarett smoking on coronary cir u-lation nd cardiac work patients ith ar teriosclerotic heart disease Ann. New York Acad Sc. 90 186, 1960

28 Hardin R A Scott J B nd Hadd F J Effect of epinephrine and norepinephrine on oronary vascular resist nce in dogs, Am J Physiol 201:276, 1961

29 Gregg D E and Sabiston, D C., J Curren research and problems of the coronary circula tion, Circulation 13:916 1956.

30 Scott J C nd Balduoras, T A. Anal si of coronary flow nd related factor following vagotom t ople nd mpathectomy Cir lation Res 7 162, 1959

31 Messer J V Wagman, R J Levine H J N ill, W A Krasnow N nd Gorlin, R J I ttern m m ocardial oxygen extraction dur ing est and exercise J Clin Invest. 41 725 1962

Case reports

Cardiac manifestations of hyperparathyroidism, with presentation of a previously unreported arrhythmia

Dieter M. Voss, M.D.
*Elliot H. Drake, M.D., F.A.C.P.***
Detroit, Mich.

The effects of hypercalcemia on the myocardium and the resulting alterations in the electrocardiogram are well known. Typical changes in individual complexes of the electrocardiogram accompanying hyperparathyroidism have been described.[1-7] Aside from prolongation of the A-V conduction and with the exception of one account of Wenckebach's phenomenon, there are no reports of advanced degrees of heart block in hyperparathyroidism. Since cardiac manifestations of hyperparathyroidism are reversible, early diagnosis and proper management are desirable. We wish to present a case of hyperparathyroidism secondary to a parathyroid adenoma, exhibiting sinus arrest with slow ventricular rates, first-degree A-V block, and bouts of paroxysmal atrial fibrillation. The records of all patients with suspected or diagnosed primary or secondary hyperparathyroidism seen at the Henry Ford Hospital during the past 20 years were reviewed. No other instance of a similar arrhythmia was found here or in a review of the literature.

Case report

A 71-year-old white man was referred to the Henry Ford Hospital on Dec. 9, 1964, from another hospital because of variable cardiac arrhythmias of 1½ month duration. He complained about "pumping of his heart," dizziness, and generalized weakness. He denied chest pain, dyspnea, or orthopnea. About 1½ months earlier he had been hospitalized for pneumonia. Marked bradycardia which was noted at that time was controlled with Isuprel. His past history suggested peptic ulcer disease. In 1953 he had renal-ureteral colics with hematuria, but a calculus was never discovered. Minimal hydronephrosis on the right side was demonstrated by x-ray examination at that time. He had had constipation all of his life and nocturia three to four times during the past 2 to 3 years. A suprapubic prostatectomy had been performed in the past. There was no history of fractures or pain in the bones.

Physical examination revealed an elderly, well-nourished and normally developed male in no apparent distress. He was edentulous. There were no signs of cardiac decompensation. No masses in the region of the neck were palpable. The heart was enlarged. No murmurs or thrills were present. The rhythm was irregular, the rate ranging between 45 and 60 per minute. Blood pressure was 160/70 mm. Hg. There was no hepatosplenomegaly. Neurologic examination was negative. Ophthalmologic examination did not show band keratopathy. Early senile cataracts were present.

Pertinent laboratory examination. White blood count 9,400, differential normal; hemoglobin, 12.7 Gm.; blood urea nitrogen 26 mg. per cent; creatinine 1.5 mg. per cent; urinalysis, pH 7.5, no albumin or sugar, calcium oxalate crystals present as well as 10-12 leukocytes; blood sugar 175 mg. per cent 2 hours after a high-carbohydrate meal

From the Division of Cardiovascular Disease, Henry Ford Hospital, Detroit, Mich.
Received for publication March 25, 1966.
*Formerly, Resident in Cardiology, Division of Cardiovascular Disease, Henry Ford Hospital, Detroit, Mich. At present, Associate Physician, Marshfield Clinic, Marshfield, Wis. Address: 630 East 4th St., Marshfield, Wis. 54449.
**Senior Associate Physician in Cardiology, Henry Ford Hospital.

Table I. Laboratory examination of patient H. V. (HFH #024 63 40)

Date	Ca (mg %)	P (mg %)	BUN (mg %)	Alkaline phosphatase (Bodansky units)
Dec. 10 1964	11.2	1.5	26	4.6
Dec. 16 1964	11.6	1.2		5.0
Jan. 3 1965	13.0	1.8		
April 3 1965	13.6	1.8	25	
April 9 1965—*Operation*				
April 10 1965	11.8	1.7		
April 15 1965	8.0	1.8		
April 26 1965	8.6	2.6		
March 7 1966	9.2	3.2		

(Glucola) calcium ranged from 11.2 to 13.0 mg per cent, phosphorus from 1.5 to 2.4 mg per cent (Table I). 24-hour determination of creatinine in the urine 1.114 mg per volume of 1,175 c.c. 24-hour determination of phosphorous in the urine 735 mg per volume, and calcium 179 mg per volume both in a volume of 1,260 c.c. The test for tubular reabsorption of phosphorous was 71 per cent.

The chest x-ray film showed some enlargement of the left ventricle and elongation of the aorta. The upper gastrointestinal series revealed an antroduodenal deformity most likely from previous inflammatory disease. The intravenous pyelogram showed a low left kidney but was otherwise negative. Examination of the skull was negative. Examination of the hands and clavicles was negative for evidence of hyperparathyroidism.

An electrocardiogram on Nov. 26, 1964 revealed atrial fibrillation with a ventricular rate of 140-160 per minute. This converted spontaneously to sinus bradycardia (Fig. 1). Subsequent serial electrocardiograms revealed basically a sinus rhythm with episodes of sinus arrest followed by nodal escape beats. At times the ventricular rate was slow as 15 per minute. Intermittent first-degree A-V block with P-R intervals up to 0.26 sec. developed (Fig.). Q-T, Q-T and Q-T were ... this normal range. The S-T segment in Leads V_{2-4} was shortened and suggestive, although not diagnostic of hypercalcemia.

A parathyroid adenoma was suspected, but in view of the cardiac status an exploratory operation was postponed. The patient was placed on a low calcium diet and followed in the outpatient department. The serum calcium increased gradually over the next 3 months, and the cardiac arrhythmia with bradycardia and intermittent sinus arrest persisted. In view of these symptoms the patient was rehospitalized on April 3, 1965. On April 9, 1965, he was operated on and an adenoma of the right lower parathyroid gland, measuring 2 by 1 by 0.5 cm. in diameter was removed. Histologically it consisted of chief cells with eosinophilic cytoplasma and occasional clear cells imbedded in fibrovascular stroma (Figs. 3 and 4). Prior to operation an intravenous Chardack-Greatbatch pacemaker had been placed and the heart was paced during the surgical procedure.

The postoperative course was uneventful. The serum calcium and the heart rhythm returned to normal. All electrocardiograms and determinations of calcium and phosphorous in the 11-month postoperative follow-up period have been normal.

Discussion

This case of hyperparathyroidism presented itself clinically with cardiac manifestations of arrhythmias and an advanced degree of A-V block. Characteristic electrocardiographic changes of hypercalcemia including hypercalcemia of hyperparathyroidism have been described as prolongation of the P-R interval, shortening of Q-T, and broad rounding of the apex of the T wave.[4,5] A shift of the T wave axis in the frontal plane has been noted to follow surgical removal of a parathyroid tumor. Accurate measurement of the Q-T interval is at times difficult. Emphasis has therefore been placed on the shortening or absence of the S-T segment resulting in a sharp upstroke of the ascending limb of the S wave which then merges with the ascending limb of the T wave.[1-4] First-degree A-V block occurred in the present case but the Q-T interval was normal. S-T changes were suggestive of hypercalcemia. The T wave axis remained unchanged after surgery. In animal experiments, increasing hypercalcemia produced an initial phase of vagal bradycardia, a second phase of tachycardia and ectopic beats, with 50 per cent dying of a ventricular fibrillation together with a final phase of slowing of the heart rate. In human beings transient sinus bradycardia, sinus arrest, and S-A block[6] have occurred during rapid intravenous injection of calcium solution. The critical toxic level of hypercalcemia is reported to be at 17 to 18 mg. per cent

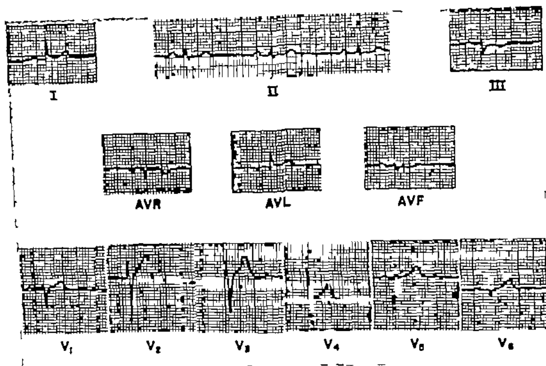


Fig. 1 Spontaneous sinus bradycardia (30/min.) follow atrial fibrillation.

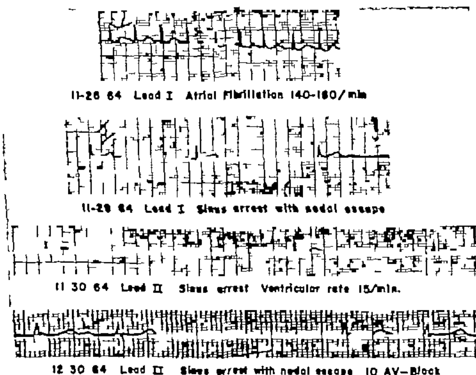


Fig. 2 Varying arrhythmia and changing A V block were the presenting symptoms of hyperparathyroidism.



Fig. 3. Section of parathyroid adenoma consisting of chief cells with eosinophilic cytoplasma and occasional clear cells imbedded in fibrovascular stroma. Hematoxylin and eosin, ×42.

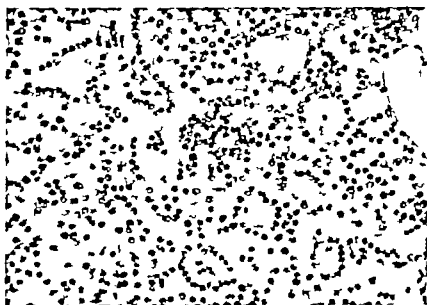


Fig. 4. Same as Fig. 3 enlarged. Hematoxylin and eosin, ×450.

The highest measured level of serum calcium in our case was 13.6 mg. per cent. It has been stated that elevation of the level of serum calcium as observed in hyperparathyroidism does not affect the cardiac rhythm.[3] One instance of Wenckebach phenomenon in a patient with hyperparathyroidism has, however, been reported. The authors of that report suggested that the Wenckebach phenomenon was probably due to excessive vagal action rather than to direct toxic action of hypercalcemia on the A-V node since it disappeared on atropinization and with anes-

therapy prior to operation Atropinization was not attempted in the present case Calcium is known to enhance the effect of digitalis and its toxic effects on the myocardium are similar to those of digitalis intoxication. The present patient never received digitalis. The mechanism for the described advanced degree of A V block has, therefore to be explained by either excessive vagal action or direct toxic action of the calcium or by a combination of both

There is no clear evidence that the episode of atrial fibrillation was due to the effect of calcium Arteriosclerotic heart disease was the most likely cause of this occurrence. From 1935 until July 1965 the diagnosis of hyperparathyroidism was recorded in 112 patients at the Henry Ford Hospital In this group there were 2 additional instances of atrial fibrillation in patients with arteriosclerotic heart disease. No other arrhythmias were observed Atrial fibrillation was found once in a series of 12 patients with hyperparathyroidism and it was associated with arteriosclerotic heart disease Recently a case was described in which a patient developed atrial flutter heart block and an apical rate of 160 per minute 2 days after removal of a parathyroid adenoma. Subsequently the patient died and the autopsy revealed another parathyroid adenoma in the mediastinum The level of calcium on the day of death was 19 mg per cent.

The treatment of primary hyperparathyroidism consists of surgical exploration and removal of the parathyroid adenoma. Hypercalcemia above the critical level of 17 mg per cent, and clinical evidence of parathyroid poisoning make the preoperative use of calcium-chelating agents advisable. In the presence of A V block and bradycardia a temporary electronic cardiac pacemaker should be used until normal A V conduction has been re-established

The present case illustrates that an advanced degree of heart block can be an additional reversible symptom of hyperparathyroidism and in combination with hypercalcemia the correct diagnosis should be suspected

Summary

A patient with primary hyperparathyroidism exhibiting A V block, sinus arrest with ventricular rates as low as 15 per minute and bouts of paroxysmal atrial fibrillation is described Removal of a parathyroid adenoma completely abolished the arrhythmias.

We believe that this is the only documented instance of this degree of conduction disturbance in clinical hyperparathyroidism

REFERENCES

1 Bradlow B. A and Segal, N Acute hyperparathyroidism with electrocardiographic changes, Brit. M J 2 197 1956.
2. Beck, G. H and Marriott H J L The electrocardiogram in hyperparathyroidism Am. J Cardiol. 3:411 1959
3 Bronsky D Dubin, A Waldstein, S. S and Kushner D S. Calcium and the electrocardiogram. II The electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcemia from various other etiologies, Am J Cardiol 7:833 1961
4. Crum W B and Till, H J Hyperparathyroidism with Wenckebach phenomenon Am J Cardiol. 6:838, 1960
5 Bronsky D Dubin, A. Kushner D S and Waldstein, S. S. Calcium and the electrocardiogram III The relationship of the intervals of the electrocardiogram to the level of serum calcium Am. J Cardiol. 6:840 1960.
6. Bellet, S Clinical disorder of the heart beat, Philadelphia 1963, Lea & Febiger p 811
7 Berliner K. The effect of calcium injections on the human heart Am. J M Sc 191 117 1936.
8 Lloyd, W D M The danger of intravenous calcium therapy Brit M J 1:662, 1928.
9 Henley R B Management of parathyroid crisis, Am. J Surg 108 183 1964
10 Lischer C. E Discussion of F R Kuster and J H Morton Parathyroid crisis, Arch Surg 91 71 1965.
11 Williams R. H Textbook of endocrinology Philadelphia, 1962, W B Saunders Company p. 855

Atrioventricular dissociation with S-A interference (ventricular capture), A-V interference (atrial capture), and reciprocating beating "Incomplete" retrograde unidirectional A-V block

Nicolaos Louvros, M.D.
Fr. X. Costeas, M.D.
Athens, Greece

Dissociation with interference is a par arrhythmia in which a faster A-V nodal or rarely a ventricular rhythm coexists with a slower sinoatrial rhythm.[1-4] In this arrhythmia it is generally accepted that *impulses from a lower center are not* conducted in a retrograde manner to the atria. The condition of the A-V node which permits conduction only from the atria to the ventricle is termed "unidirectional block." It is a complete retrograde A-V block and in the arrhythmia under discussion, is considered to be a physiologic phenomenon. On the other hand some *sinus* impulses reach the ventricle at a time when it is no longer refractory and can activate it; this produces S-A interference or ventricular capture. At all other times the ventricles are *stimulated by impulses* originating in the A-V nodal (or rarely ventricular) center.[1-4]

The following case report seems to be particularly suitable for the presentation of this interesting arrhythmia because S-A interference alternated with A-V interference and return extrasystoles. In so far as we know this combination has never been reported previously. The underlying mechanism is discussed.

Case report

K. K., a 35-year-old white man was under observation at the Red Cross Hospital from Feb. 24, 1965, until he died on May 24, 1965. He had chronic glomerulonephritis and fibrinous pericarditis, with pericardial tamponade as a terminal event.

His final admission was between May 22 and May 24, 1965, for dyspnea and orthopnea. He also had some dry cough, precordial pain, irrational behavior, and restlessness.

At the time of his admission he was cyanotic and had greatly distended neck veins. In addition, physical examination revealed a blood pressure of 100/80 mm. Hg, soft and irregular peripheral pulse at a rate of 100 per minute, a respiratory rate of 45 per minute, a temperature of 37.5°C, muffled heart sounds, irregular cardiac rhythm, and a to-and-fro, characteristic pericardial rub. The liver was 2 fingerbreadths below the right costal margin and was tender. Moderate edema in the lower extremities was noted.

Routine laboratory examination revealed leukocytosis (leukocytes 15,300 per cubic millimeter), normochromic and normocytic anemia (erythrocytes 3,800,000 per cubic millimeter and hemoglobin of 9.5 Gm. per 100 ml.), azotemia

From the Cardiovascular Department, Red Cross Hospital, Athens, Greece.
Received for publication April 6, 1966.
Address: 3 Sekeri St., Athens (134), Greece.

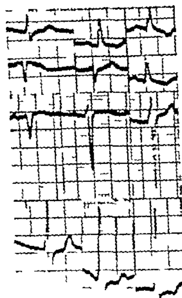


Fig 1 Electrocardiogram (the standard leads, the unipolar limb leads, and the precordial leads). Full description in text

(blood urea nitrogen of 450 mg per 100 ml), and hyperpotassemia (8.2 mEq /L.).

A chest film showed an enlarged cardiac silhouette of "water bottle" shape with blunting of the cardiophrenic angle, and shortening and widening of the supracardiac shadow The lung fields were clear

The electrocardiogram (Fig 1) taken on May 22, 1965, show (1) P waves of very low voltage (2) T waves peaked, symmetrical, but not tall, as seen in Leads V and V diphasic (− + type), seen in Lead V inverted in diffuse manner as seen in Leads III V and V_6, (3) elevation of the S-T segment, as seen in Leads V V_2 and V_3, and depression of the S-T segment, as seen in Leads V and V

These findings suggested the combination of pericarditis and hyperkalemia.

Apart from the above-mentioned features complicated kind of arrhythmia was also present, but it could not be analyzed in the standard leads, the unipolar limb leads, or the precordial leads.

The rhythm is better seen on the second strip of Fig 4 where Lead III is shown. In this tracing trigeminal rhythm can be seen, but the mechanism of this arrhythmia remains unclear Therefore an esophageal electrocardiogram was obtained. Cuttings from the same electrocardiogram are shown in Figs. 2 3 4 and 5.

Analysis of the ECG

The dominant rhythm is interference dissociation between a sinus arrhythmia and an A V nodal rhythm The interatrial cycle length varies from 0.35 to 0.48 second In the continuous strip of Fig 2 P_1 P_2, P_3, P_4, and P_5 demonstrate S-A interference After P either an intermittent S-A block or sinus arrest prevents the atrial discharge. Indeed in the successive intervals between the sinus P waves, 4 2 4 6 6 and 2 P waves are lost As an effect of this abnormality the A V nodal center becomes the dominant pacemaker for the ventricle A V dissociation with interference is established The occasionally conducted S-A impulse passing through the A V node discharges its pacemaker so that the formation of impulses there begins again at the same rate as during the periods without interference. The subsequent A V nodal beat comes at the expected time and depolarizes both ventricles and atria Thus an A V nodal interference ensues, the atria being depolarized in a retrograde manner The next two or three nodal beats do not stimulate the atria. Indeed their retrograde conduction to the atria is either impaired (A V nodal impulses which correspond to the ventricular complexes R_4, R R, R, R, R, R_{27}) or prevented by the sinus impulse and a collision takes place between the retrograde and the antegrade impulse below the atrial level in the A V junction (A V nodal impulses which correspond to the ventricular complexes R_6, R R, R R_{26}) The A V nodal impulses which produce the ventricular complexes R R and R_{23} are conducted to the atria but reenter the ventricles, producing the ventricular complexes R, R, and R, respectively Systoles of this kind are known as return extrasystoles. Here the same A V nodal impulses produce an A V interference which is followed by an S-A interference Because of a delay in the early reciprocal impulse below the site of the A V nodal pacemaker the shortening of the first nodal cycle after a return extrasystole is due to a change in conduction time and not to an irregularity of the nodal discharge. The same phenomena are repeated in Figs. 3 4 and 5 In Fig 4 the alternation of S-A interferences with return extrasystoles creates a trigeminal rhythm A difference is noted only in Fig 5 where a sinus impulse P_9, activates the ventricles, producing the ventricular complex R The same impulse returns, soon after in the A V node and



[illegible]

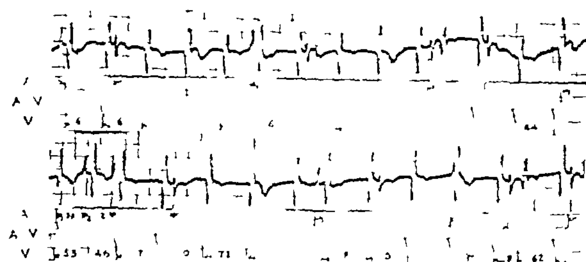


Fig 3 Electrocardiogram [illegible] strips [illegible] lead [illegible] 149 m [illegible] the narrowly [illegible] rhythm [illegible] The [illegible] representation explaining clearly the underlying mechanism

reactivates the atria producing the retrograde P wave (re-entry of the sinus impulse to the atria). This phenomenon has been called "atrial return extrasystole."[7] But the reciprocating beating continues and the atrial excitation has the chance to reactivate the ventricles. R indicates the result of the movement and shows a return extrasystole to the ventricles. In other words, the same sinus impulse produces in succession an S-A interference, ventricular interference, and an atrial interference.

Comment. The P waves are classified into antegrade and retrograde ones according to their morphology. The antegrade P waves are upright, but the retrograde ones consist of a smaller positive and a greater negative deflection.

The depression seen occasionally in the A-V nodal beats is caused by the atrial de-

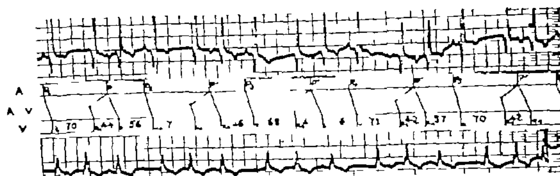


Fig 4 Electrocardiogram (esophageal lead, obtained t electro le level 40 cm. from the nares and Standard Lead III). The diagrammatic representation explains learly the nderlying mechanism of the trigemi nal rhythm. F ll description in text.

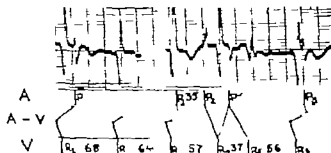


Fig 5 Electrocardiogram (esophageal lead obtained at electrode level 40 cm from the nares). I this figure, he reciprocating beating is shown learly (P R4, P' R). F ll description in text.

polarization wave (T) Typical examples of the T waves are often seen all over the esophageal electrocardiogram as after P4, I4, P P4, etc n Fig 2 and after P I4, etc in Fig 3

Discussion

In A V d ssociation with nterference the complete unidirectional retrograde A V block s an indispensable feature. Thus in this arrhythmia it is mpossible to have A V (or entricular) interference The absence of this block would ha e as a result the development of an A V rhythm The difference between these two arrhythmias consists only n the presence or absence of this retrograde block. The mechanism of this block not completely understood Mol is[14] postulated that in A V dissociation with interference the A V nodal stimuli r of inadequat intensity and cannot pas the junction between the A V node and the atrial muscle On the contrary in A V block with V A conduction the uni directional A V block is antegrade so that it is possible to have A V (or entricular) nterferences Winternitz and Langendorf called th is interest ng and unusual phenomenon nterference-dissociation between entricle and auricle

In the case under discussion the high level of serum potassium produces an S-A block occurring t irregular intervals and as a result of this, a dissociation by de f ult," passive form or passi e heter otopy of th A V center ensues The S-A interferences, and the relationsh p between the S-A mpulses and th A V nodal ones, prove normal A V conduct t The r regular conduction of the A V nodal beats to the atria signifies the development of an ncomplet unid ectional retrograde A V block. Henc few A V nodal beats are conducted to the atria, and the A V dissocia-

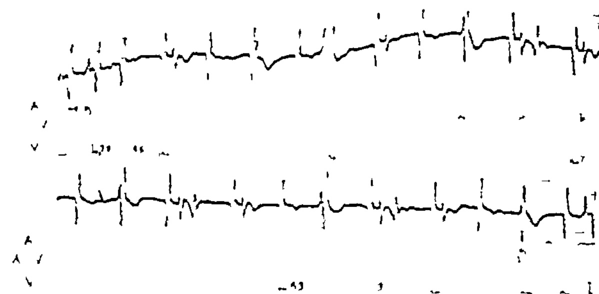


Fig. [illegible] (cm from the nares [illegible])

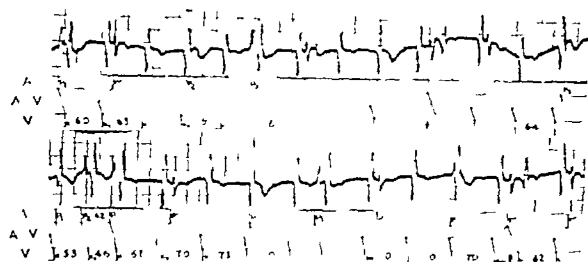


Fig. 3. Electrocardiogram [illegible] different [illegible] esophageal lead [illegible] level 43 cm from the nares), showing additional instances of the rhythm under discussion. The diagrammatic representation explains [illegible] the underlying mechanism.

reactivates the atria producing the retrograde P'' wave (reentry of the sinus impulse to the atria). This phenomenon has been called "atrial return extrasystole."[?] But the reciprocating beating continues and the atrial excitation has the chance to reactivate the ventricles. R indicates the result of the movement and shows a return extrasystole to the ventricles. *In other words* the same sinus impulse produces in

succession an S-A interference, a ventricular *interference and an atrial interference.*

Comment. The P waves are classified into antegrade and retrograde ones according to their morphology. The antegrade P waves are upright but the retrograde ones consist of a smaller positive and a greater negative deflection.

The depression seen occasionally *in the* A-V nodal beat is caused by the atrial de

Clinical pathologic conference

Benjamin M. Kaplan, M.D.
Alfred Pick, M.D.
Conrad L. Pirani, M.D.
Chicago, Ill.

History

A 72-year-old white woman was admitted to Michael Reese Hospital and Medical Center on Aug. 26, 1965. She was hospitalized for 10 weeks. Her chief complaint was severe substernal pain radiating into both arms accompanied by sweating, nausea, and vomiting. The pain had been present for some hours during the night before admission and had recurred for 6 hours on the day of admission. She also experienced shortness of breath. She had not had similar chest pain previously.

The relevant past history of this patient included radical left mastectomy in 1951 for carcinoma of the breast with axillary lymph node metastases. In 1963 she complained of cough, dyspnea, and loss of weight of 10 pounds. A left pleural effusion was diagnosed and the pleural fluid was found to contain malignant cells. Skeletal x-ray survey was normal at that time. In 1964 androgen therapy was started, with good clinical response in that she felt stronger, there was a decrease in her cough and shortness of breath, and her chest x-ray film remained stable with no reaccumulation of pleural fluid. She had also had mild hypertension for many years as well as internal strabismus since 1959. Both of these conditions had been fully investigated and no etiological factors were found. Her thyroid function had been evaluated and found to be normal.

Physical examination at the time of admission of the patient to the hospital showed that she was an elderly woman who was severely virilized. The blood pressure was 180/110 mm. Hg, and the pulse was 88 per minute, regular, and of good volume. She had left internal strabismus with left ptosis. She was not in congestive cardiac failure. There was dullness to percussion at the base of the left lung with decreased entry of air in the left lower lobe. No adventitious pulmonary sounds were heard. The scar of the radical mastectomy was seen on the left.

Two days after admission, a to-and-fro apical pericardial friction rub was heard. Her white blood count was 13,100 per cubic millimeter with a shift to the left. She developed a fever of 100°F orally; this persisted for the first 2 weeks, and thereafter she remained afebrile.

The chest x-ray film at the time of admission showed normal heart size, and clear lung fields except for blunting of the left costophrenic angle and some pleural thickening in this area. The patient's heart rate was regular between 95 and 100 per minute and this persisted throughout her hospital stay. Her blood pressure always remained within normal limits, except for the initial elevation found at the time of admission.

Three days after admission it was thought that she demonstrated signs of mild congestive heart failure and she was digitalized. She was also anticoagulated, and prothrombin times were kept within the therapeutic range with warfarin sodium. The pericardial friction rub that appeared 2 days after admission lasted for 3 days, then disappeared for 4 days, after which it reappeared and was then persistently present up to and after the time of her discharge from the hospital. Her blood urea nitrogen rose to 35 mg. per cent, and her serum creatinine to 1.5 mg. per cent. Anticoagulation therapy was stopped on Sept. 8, 1965, because her hematocrit had fallen from the admission level of 50 per cent to 37 per cent. No site of hemorrhage was found.

On September 8, chest x-ray films showed marked increase in the size of the heart shadow and bilateral pleural effusions. A chest x-ray film on September 10, showed a further increase in heart size. There was no clinical evidence of cardiac tamponade. An echocardiogram revealed no pericardial effusion. Because of the mild elevation of

With the participation of Bertram Levin, M.D. (Radiology) and Bernard [illegible], M.D. (Medicine).

Received for publication June 11, 1966.

*Department of Medicine, Division of Cardiovascular Diseases, Michael Reese Hospital and Medical Center, Chicago, Ill.

**Department of Pathology, Michael Reese Hospital and Medical Center, Chicago, Ill.

Address correspondence to Dr. Benjamin M. Kaplan, Dept. of Medicine, Division of Cardiovascular Diseases, Michael Reese Hospital and Medical Center, 29th St. and Ellis Ave., Chicago, Ill.

temper ture un sing l l ter l phur l d ms nd pericar lial rul t w be l t that she ffered f om Dressle ph nom non nd ther j th 40 mg of pred ne pe da w t ted She be me f l le nd her ma ked lm e the pl u l ff on Aldacta t A 25 mg three times da h l les t ted S d ef the pred sone f th med t n t ued throught t th Oct ber l ber l ng t ld were back t the t t th the h l t t th t me f her admis on nd the nt mg l h l m kedl de cr sed

During the ur t fo f h s hosp t liz the SGOT SGPT nd LDH levels ere ll t wh t be ma kedl lev ted l lect c rd gr ph t n ges t ken frequent er l howed ten n t sm l l p ersion ll fluid f t on h p ent k on f he S T segment rest g ent la neurs m She f ha ged m N v 3 1965

The p tie t readmit ed on Dec 29 1965 mpl ining f pre l g n l ing the 2 week l fore adm sion The da before adm ss n she had suffered sever retroster l pa n panied by omiting nd t ng nd h l fee f nt l ha g l pulse he had been ma ena doses f 10 mg f pred one 25 mg f Aldactazide A nd 0 25 mg of Lanox pe l

On xamination he w ery d pnei nd les me nt f st given n ge ll extremities wer old The bl l pre w 110 0 mm Hg nd th pulse t ated bet ee per d of 110 pe m t nd 45 t 50 per min t h hm eg lar Her neck eins er l t nded A h l eject n syst l m mur w he rd over ll f the precor l m nd there w per rdial f tion d at the pex There was pr t fu tof g llop (abe t) tudies t this t me rev led hemoglob 13 8 Gm per en wh t bl od ell ou t 15 000 (86 pol l blood ure nitrogen 37 g per ent re t nin 1 7 mg per t N 1 6 Cl 86 k 3 7 CO 17)

Her he rt t ontinued t ry bet een 40 nd 100 per min te Slow nf on of 2 mg f Isuprel in 1,000 of 5 per ent dextrose in w t usuall accelerated the ent l hythm but in the night fter admission that was unsuc essf l nd the patient died probabl f entricula y tole

DR. GOLDB Dr Benj mi Kapl w ll discus the cl ical pect of this se

Discussion

DR. KAPLAN To summarize briefly we are considering a 72 year-old woman who in 1951 at the age of 58 underwent a radical left mastectomy for a carcinoma of the breast with axillary metastases. There is no mention in the protocol of x ray therapy after this procedure This is perti nent since recently myocardial infarction due to postradiation fibrosis of the coronary arteries after x ray therapy to the chest has been reported[1] *In* 1959 the patient wa studied *for internal str l osmus*, but no pecific etiol gy wa found In 1963 12 years after the ori nal operation clini al *manifestations* of m ta tases to the left pleura were noted and cytological studies r vealed malignant cell in the left pl ural fluid At thi time androgens were begun and the patient experienced definite improvement

On Au (1965 about 2 years later th patient entered Michael Reese Hospital with the clinical pi ture of acute myocardial infarction manifested by severe chest pain, *sweating and vomiting* Two day after admi ion he w s found to have a peri ardial friction rub leukocytos with a shift to th l ft and a low-grade fever The foll wing da she h wed sign of conges tive heart failure at which time digitalis and antiarrhythmic therapy were begun The peric rdial friction rub which had been heard day after admi ion had disap peared but recurred period cally through ut the h spit l tay Approximat ly 2 week after she had been admitted to the hospital there was evidence of an enl rged ardiac shadow lnlater l pleural effusion and an anemia The impression was that of the Dressler s syndrome or post myocardial infarction syndrome At thi time corticosteroids were begun and the patient experienced an excellent response to this therapy She left the hospital on Nov 3 1965

About month later the patient was readmitted in severe di tress characterized by dyspnea retrosternal pain vomiting diaphoresis, and an arrhythmia A peri cardial friction rub was again noted a well as a gallop rhythm and for the first time a prominent ejection systolic murmur was heard throughout the entire precordium The serum enzymes were ele vated a mild azotemia was present and the serum electrolytes suggested *hemodilu* tion Initially the patient improved with the use of intr venou Isuprel but died the following day

The electrocardiograms of both hospital admissions will be dealt with in great detail subsequently by Dr Fick

Dr Levin will you please discuss the x ray films.

DR. LEVIN (Interpreting the x ray films) The base-line chest film that we have is

from 1959 and the heart size is normal the lung fields are clear there is no evidence of a pleural reaction the left breast is absent

In April 1962 (Fig 1 *top*) there was some persistent consolidation of the left lower lobe not present in 1959 with a small pleural component representing a localized minimal effusion or pleural scarring I do not know whether this was a chronic pneumonia or the residue of an old pulmonary infarct.

Then in November 1963 when the patient was rehospitalized there was a large left pleural effusion Discussion of the differential diagnosis of these x ray findings is unnecessary since we know that this was a malignant effusion. The lung fields were not remarkable.

In August 1963 a bedside film was obtained while the patient was lying supine In this position the heart size was not remarkable but left pleural effusion was present. Another film 2 weeks later (Fig 1 *center*) showed appreciable enlargement of the cardiac density with bilateral pleural effusion but no vascular congestion. In spite of the fact that at this time the echocardiogram was reported to be negative I think that there was pericardial effusion It is of interest that at about this time the anticoagulant was stopped because there was a marked drop in hemoglobin According to the protocol no evidence of bleeding was found I wonder whether possibly there was bleeding into the pericardium

In an upright film 5 days later the cardiac size was somewhat smaller with bilateral pleural effusions but completely clear lung fields. Fourteen days later (Fig 1 *bottom*) the pleural effusion had disappeared almost completely and the central mediastinal figure was smaller From then on a further decrease in heart size to almost the original dimension was noted The last film in November 1963 showed the consolidation in the left lower lobe that had been seen initially in 1962 and recurrence of a small right pleural effusion the left pleural reaction was unchanged

DR PICK (interpreting the electrocardiograms) In the course of the entire observation 16 electrocardiograms were obtained on this patient. Three in 1956 196 and 1963 were normal in every respect. Three subsequent selected records of September



Fig 1 Chest x-ray films on April 30 1962 (top), Sept. 14 1963 (*center*), and Oct 27 1963 (*bottom*)

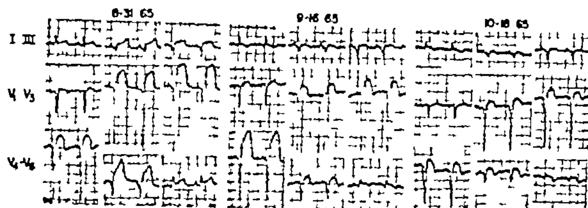


Fig. Electrocardiogram See text

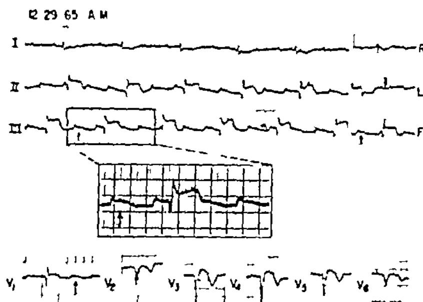


Fig 3 Electrocardiogram (The framed portion of III reproduced enlarged (about double size) See text

and October 1965 after the first attack of severe chest pain are reproduced in Fig 2 They show during sinus rhythm with a normal P R interval the characteristic features of a recent myocardial infarction with extensive destruction of tissue in the anterolateral and posterior walls, as revealed by the QS or QR waves in limb and precordial leads. The marked concordant S-T deviations in all of these leads are in keeping with the effects of diffuse recent injury in these regions and/or an associated pericarditis. In records obtained 2 and 10 weeks after the first the development of ischemic T inversions can be noted in Leads I II V_4 and V but the S-T deviations persist This could be due to persistence or recurrence of the pericardial process to digitalization or to the development of a ventricular aneurysm

Fig 3 is a record obtained in the morning after the second admission and here the following additional abnormalities are noted Atrial and ventricular action are regular but completely dissociated the former faster (115) than the latter (43)

indicating a high degree of A V block, possibly complete A V block. The descending limbs of the P waves do not return to the base line but merge with displaced T segments that are elevated in Leads II III aV F and V_1 and depressed in Lead aV_L (indicated by the upright and inverted arrows) Thus an atrial injury vector is present pointing to the right, superiorly and anteriorly The ventricular complexes have maintained the basic abnormal configuration indicating a supra ventricular (A V junctional) pacemaker but the QRS is more slurred and slightly prolonged to 0 12 sec. with a distinct R in Lead V S-T elevations are now most prominent in Leads II III and aV The T waves on the other hand are no longer inverted in Leads I and II but broader and more inverted in Leads V to V_6. Thus it would appear that the residue of the previous extensive transmural infarction possibly associated with a ventricular aneurysm is modified by new injury effects and probably additional infarction involving the high posterior wall the right atrium and the ventricular septum including specific fibers of the A V junction and of the right bundle branch On the basis of all this a prediction could be ventured of the location of the most recent obstruction in the coronary tree to be found by the pathologist. It would be at or proximal to the cross of the heart, where the ramus septi fibrosi takes off at about a right angle from the coronary branch that supplies the posterior wall of the left ventricle

In the record obtained in the afternoon of the same day (Fig 4) the ventricular rate has accelerated to 104 and at first glance it would appear that there is a simple sinus tachycardia. However closer examination reveals that the P R interval varies while the ventricular action remains precisely regular (compare Leads V_1 and V_2 with Lead V_3 and V) Thus actually there is still complete isorhythmic" A V dissociation caused by constant collision in the A V junction of antegrade sinus and retrograde ectopic impulses both accelerated to about the same range However only the sinus cycles are slightly variable—causing the apparent P R variations. The probable continued presence of a high degree of A V block cannot be recognized in this record Apart from less T inversion in precordial leads, no additional alterations are noted in the P waves and QRS complexes or in the S-T and T segments.

The final record on December 30 (Fig 5) is distorted by extracardiac artefacts recurring in the longer Leads II and III at the indicated cycle of about 2.3 sec Thus labored respiration at a rate of about 27 per minute can be diagnosed in this electrocardiogram. Although the atrial rate is as fast as before (104 per minute) the regular ventricular action has slowed to 80 and complete A V dissociation with A V block is once again clearly evident. More marked

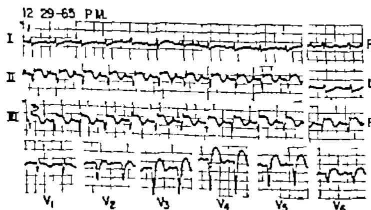


Fig 4 Electrocardiogram. See text.

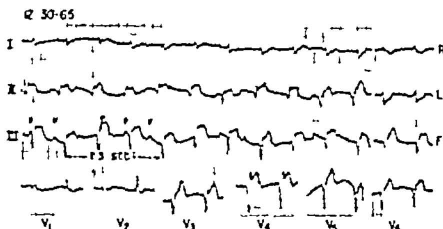


Fig. 5. Electrocardiogram. The ... one respiratory cycle.

S-T deviation, especially in Lead II, III, aVF, and VF, indicates persistent and increasing injury of the posterior and lateral walls, perhaps leading to extension of the infarcted area.

It is of interest from the standpoint of understanding the cardiac mechanism during the terminal episode to compare the ventricular rates in Figs. 3-5 listed in Table I. The different rates on the three occasions can be reduced to a common denominator, a cycle of about 20, corresponding to a rate of 300. Thus it can be surmised that in all three tracings the same A-V junctional tachycardia may have been present with complete retrograde and varying antegrade blocks. The latter was responsible for the differences in the manifest ventricular rate. On the morning of December 29, a 7:1 block caused the slowest rate of 43; in the afternoon of December 29, a 3:1 block caused the fastest rate of 104; and on December 30, a 4:1 block caused an intermediate rate of 76. These variations in conductivity in the distal part of the A-V junction could be a manifestation of varying states of ischemia or, conceivably, of varying effects of the infusion of isoproterenol.

My interpretation of these electrocardiograms was based on the assumption that the alterations in rhythm and contour were caused entirely by a progressive occlusive, most likely atherosclerotic, process of the coronary arteries. However, Dr. Kaplan may have different ideas about a possible etiology of these diverse electrocardiographic abnormalities.

DR. KAPLAN: I have been asked whether the androgen that the patient received could have had any effect on her coronary atherosclerosis. Substantial laboratory and clinical evidence has been accumulated in the Cardiovascular Institute of this institution and elsewhere to indicate that estrogens may have a protective effect against clinical atherosclerotic coronary heart disease. However, the corollary, namely, that androgens may accelerate atherogenesis, has never been demonstrated. Recently, Dr. Jain, Dr. Ruth Lick, and Dr. Katz have shown that testosterone can counteract the increased hypercholesterolemia and atherogenic effects of a low protein diet in chickens.[4] Others have shown that testosterone may lower the levels of serum

Table I

	December 29		December 30
	Morning	Afternoon	
Atrial rate	115	100-101	101
Ventricular rate	43	104	80
Ventricular cycle	140 (7 × 20)	57 (3 × 19)	76 (4 × 19)

cholesterol in human beings.[3] Thus, there is no evidence to my knowledge that androgens, per se, play a significant role in the production of coronary heart disease.

The patient whose case is being discussed today had at least three different types of pericarditis. First, the pericarditis that occurred 2 days after the acute myocardial infarction was the so-called "epistenocardia." Characteristically, the pericardial rub occurred on the second or third day after the infarction and disappeared within a few days. This pericarditis was not associated with any significant systemic alterations, such as high fever, anemia, gross pericardial effusion, pleural effusion or pneumonitis. The second type of pericarditis was that of metastases to the pericardium, which will subsequently be discussed in detail. The third source of pericarditis was Dressler's or the postmyocardial infarction syndrome.[4] Typically, the pericardial friction rub occurred on the fifteenth postinfarction day and was associated with a pleural effusion, pericardial effusion, anemia, and fever. The response to corticosteroids was very dramatic. Of interest to me is whether metastases to the myocardium with or without pericardial involvement can produce the Dressler syndrome. We know that patients with an implanted pacemaker in the myocardium, stab wounds of the heart, or a heart paced percutaneously through needles in the myocardium have developed this characteristic syndrome, not at the time of the damage to the heart, but weeks later. A fourth consideration for pericarditis would be a small rupture of the atrium or ventricle.

With regard to the A-V block, it is well known that A-V block occurs acutely after atherosclerotic coronary occlusion with resulting myocardial infarction and involvement of the A-V node or *bundle* branches. In addition, cases have been reported in the literature in which invasion of the conduction system by tumor has given rise to destruction of the A-V node, and the S-A node, and produced bundle branch block, A-V block, and the Stokes-Adams syndrome.

Atrial infarction, as Dr. Fick indicated, is often overlooked. There are *actually* several causes of atrial infarction, usually the etiology is coronary atherosclerosis. However, atrial infarction has been reported in such conditions as periarteritis nodosa, bacterial endocarditis, and in some congenital lesions in which there have been single coronary arteries. It is of more than academic interest that we try to establish the diagnosis of atrial infarction. At least 80 to 85 per cent of atrial infarctions have associated atrial thrombi,[7] which may give rise to either pulmonary or systemic embolic phenomena, or both. Whether one does or does not use anticoagulants routinely with acute myocardial infarction, in the presence of atrial infarction one would be obliged to institute anticoagulants because of the high incidence of mural thrombi. The diagnosis of atrial infarction is made by (1) the characteristic alteration of the T segment, (2) changes in the atrial mechanism, such as atrial premature beats, atrial fibrillation, flutter, etc., with day-to-day changes, (3) A-V block, (4) change in the contour of the P wave, and (5) concurrent presence of ventricular infarction.

It is said that about 5 to 10 per cent of all metastatic malignant neoplasms throughout the body involve the heart, including the pericardium.[8] Metastases to the heart muscle per se are usually asymptomatic, and, as a rule, the diagnosis of cardiac metastases is made by signs and symptoms relating to pericardial metastases. Metastatic tumors that frequently involve the pericardium are bronchogenic carcinoma, carcinoma of the breast, and leukemic infiltrates. Characteristically, there are a pericardial friction rub and effusion, but rarely cardiac tamponade. The pericardial fluid usually discloses malignant cells and shows a markedly elevated level of lactic dehydrogenase. Should metastases involve the myocardium, nonspecific electrocardiographic changes or those of a myocardial infarction may be seen. In addition, cases are on record of persistent elevations of ST-T or the T segment suggestive of a ventricular aneurysm and or atrial infarction which was due to metastases to the heart muscle. This finding would certainly fit the case being discussed today. As I mentioned previously, metastatic lesions may involve the conduction system and produce various types of arrhythmias, including A-V block, paroxysmal tachy-

cardia etc Should the tumor encroach upon the coronary arteries an *ina pectoris* may be present Meta tatic tumors that involve the endocardium simulate valvular heart disease by obstructing orifices In the case discu sed today th patient was described as having a *promin nt ejection* systolic murmur at the time of the last admi ion to the hospital This ug ests that the tumor ma have partially occluded either the ortic or pulm in ry ariti e producing a rel tive *tenosi On other pos i* bility for the n urmur i th at of a marantic endocarditi

Tumor emboli t the coronary arteries merit con deration however a definite diagnosis of thi *condition* i only *made* by the pathologi t

M ram Edeli t Luria and Miller from thi in titution found that about 1 5 per cent of all heart with myocardial in farctions at autopsy had ventricular an eurysm Thu this condition i not rare In this case in ad lition to th usual cause of ventricular aneurysm nam ly coronary atherosclerotic heart disease and myocar dial infarction the pos ibility of a meta static lesion to the heart producing weak ness of th ventricular wall mu t be con idered

In conclusion I think that the major problem in the present case is that of an obstructive disease of the coronary arteries with resulting myocardial infarction Is thi due to atherosclerosis, tumor emboli or invasion of the coronary arteries from with out by a tumor There i also evidence of recurrent pericard tis from at lea t three causes. In addition we have clinical find *ings of invasion of the conduction system* either by tumor or by infarction and fibrosis. There i also electrocardiographic evidence to suggest either atrial infarction or a ventricular aneurysm or both Finally *the terminal* event could have been due to a rupture of the atrial wall or ventricular muscle I will list my final diagnoses as follows (1) Severe coronary atherosclerosis with infarction of the *anterior and posteroinferior walls of the* left ventricle, as well as atrial infarction. (2) Metastasis of breast carcinoma to the pericardium myocardium and endocardium. *(3) Invasion of* the conduction system of the heart by neoplasm (4) Ventricular aneurysm (5) Atrial and/or ventricular rupture? (6) Metastasis of brea t carcinoma to the pleura and lung

DR GOLDEN Dr Eisen tein as one of the physi ians who atten led thi patient will you please comment on the clinical course

DR EISENSTEIN There are several addi tional factors E trogens which we con *idered to be the drug of choice in a woman of this age were tried initially When she* could not tolerate them we changed to androgen therapy and the resp onse was bsolutely dramatic Wherea 2 years be *fore her death the patient had been failing* had been lo ing weight and had been markedly d spneic she now had a notice able symptomatic improvement gained wei ht, and her condition stabilized Her *entire linical course was marked by* dyspnea out of proportion to the pul monary findin and we thou ht that she had exten ive pleural meta tases perhaps with involvement of the lymphatics This patient demon trates that, when the in terval between the primary carcinoma of the brea t and the appearance of meta tases i long there is an excellent hance of re sponse to any change in the hormonal milieu be it androgen estrogen or even cortisone It i remarkable that ll we ever saw on the x ray films was a small amount of blunting of the left pleural cost ophrenic an le despite the fact that I am sure she had consider ible pulmonary meta tases

The patient was receiving maximum therapy for cardiac failure without any *effect on the pleural effusion and the cardiomegaly* Within 1 week after prednisone therapy was added she had resorption of the effu ions and a marked decrease in heart size which to u represented a re markable response and we thought that this favored the diagnosis of a Dressler phenomenon

DR. ROSENBLATT In view of the anterior and posterior wall infarctions, could the murmur represent the development of perforation of the ventricular septum?

DR. KAPLAN I cons dered that. *Usually this entity is associated with a regurgitant* murmur and not an ejection murmur The other consideration for the sudden appear ance of a systolic murmur would be the rupture of a papillary muscle However this is likewise associated with a regurgitant murmur

DR. MILLER I agree with the diagnosis that Dr Kaplan presented *However in*

scanning the protocol I thought of another type of invasion that merits some consideration and that is dissection of an aortic aneurysm There are a number of things here that could fit with this diagnosis, including the myocardial infarction the pericardial hemorrhage, and the murmur I do not know how to dismiss this possibility

DR. KAPLAN Yes, I think that dissection is possible. It is always a hard diagnosis to exclude In the literature, I found no reports of metastases to the aorta but perhaps it occurs.

DR. GOLDEN Any other questions? Dr Pirani what were the necropsy findings?

DR. PIRANI Postmortem examination revealed a woman who was well nourished and had marked evidence of masculinization hirsutism of the face trunk legs and slight hypertrophy of the clitoris. The skin had a mottled appearance over the trunk and arms and contained a number of small hemorrhages which are unexplained There was the scar of a radical left mastectomy The right breast was grossly normal but, histologically fibrocystic disease was present.

The abdominal cavity was entirely negative.

There was some fluid in both pleural spaces about 150 ml in the right, and 200 ml in the left. The left pleural space was almost completely obliterated by fibrous adhesions, which in some areas appeared to be somewhat nodular These nodules



Fig 6 The opened heart reveals the outflow tract of the left ventricle N t the large aneurysm filled th thrombi involving the anteroseptal all t the sit of an old myocardial infarct. The pericardium is covered by fibrous tags and studded with numerous poorly defined t mor nodules. The ascending orta, about 2 cm abov the aortic valv is somewhat narrowed by the neoplastic invol ement of the pericardium nd periaortic tissue

were gray white firm and measuring 1 up t 1 cm in diameter. The pericardial cavity was almost completely obliterated by dense fibrous adhesions within which, especially over the posterior surface of the heart, were many fairly well-circumscribed nodules similar to those observed in the pleura and strongly suggestive of tumor metastases.

The heart was moderately enlarged (Fig. 6). The precise weight could not be determined because of the severe pericarditis but was estimated to be about 450 to 500 grams. The left ventricular wall measured up to 1.6 cm in thickness. In the anterior wall of the left ventricle near the apex there was a rather large aneurysm measuring about 5 cm in diameter and filled by an organizing thrombus. The wall of the left ventricle in the region of the aneurysm measured 0.4 cm in thickness. All cardiac chambers were moderately dilated. The valves were normal except for slight fibrous thickening of the mitral leaflets. Histologically a cross section of the aneurysm disclosed an organizing thrombus well adherent to the endocardium and marked fibrosis of the wall. Small groups of intact muscle fibers were present in the fibrous connective tissue. This is a relative common finding in old myocardial infarcts and to the best of my knowledge has not been satisfactorily explained. Elsewhere the myocardial fibers were moderately hypertrophied. The coronary arteries had a normal distribution and were markedly atherosclerotic. The anterior descending branch was completely occluded by an old fibrotic process 1 cm below the bifurcation. The main right coronary artery was also occluded by a more recent thrombus which grossly was red-brown and was located about cm from the aorta. Histologically the thrombus was seen to have developed at the level of a large atheromatous plaque which had already severely narrowed the lumen of this vessel. In the posterior wall of the left ventricle there was

Large recent infarct which extended into the superior and posterior portion of the interventricular septum. In this area the myocardial fibers exhibited early necrotic changes with loss of nuclei and loss of normal staining qualities. This w

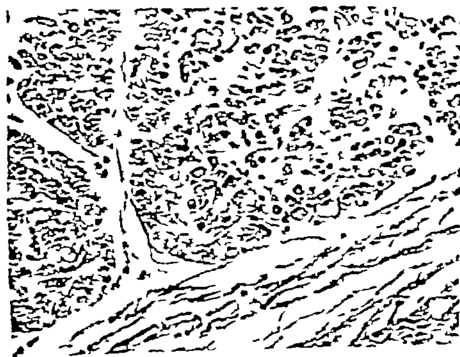


Fig. 7. Acute myocardial necrosis in the wall of the right atrium. Note the abnormal staining qualities of the muscle fibers. Hematoxylin-eosin. ×300

ciated with numerous interstitial infiltrates of polymorphonuclear leukocytes. This infarct was considered to be 2 days old. Similar areas of recent infarction were also present in the posterior wall of the right atrium (Fig. 7). It is interesting to note that the damaged myocardial fibers in the region of recent infarction exhibited a strongly positive PAS reaction. In view of the well-known loss of glycogen from muscle fibers that occurs as a result of ischemia, this has been attributed to the accumulation of water-insoluble glycoproteins.[11]

Dissection of the conduction system[12] was limited to the A-V node and the bundle of His. In appropriate sections the A-V node could be easily identified as a roughly oval-shaped structure in the wall of the right atrium and the bundle of His as a triangular structure in the wall of the right ventricle (Fig. 8). Under higher magnification both structures were seen to be composed of relatively small fibers with the appearance of premature or fetal muscle fibers separated from the adjacent myocardium by a thin layer of fibrous connective tissue. The A-V node, except for mild interstitial fibrosis, was normal (Fig. 9). The bundle of His, on the other hand, was adjacent to and partially included in the area of recent infarction involving the posterior portion of the interventricular septum. Early necrosis of the fibers and interstitial fibrosis were present in the bundle (Figs. 10A and 10B). The adjacent myocardium was also the site of interstitial fibrosis, with small foci of calcification, findings which were interpreted as evidence of an older ischemic process. A small artery in the bundle of His exhibited only mild sclerosis of its wall.

James[13] has written extensively on the anatomy of the coronary arteries with particular regard to the blood supply of the sinus node and the atrioventricular node. In approximately 90 per cent of the hearts the coronary artery that supplies the A-V node and the bundle of His is a branch of the right coronary artery originating from this vessel where it begins its posterior descending course, the so-called crux of the heart. On the other hand, the artery to the sinus node originates from the right circumflex coronary artery in 55

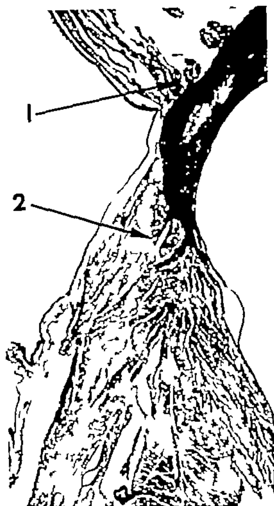


Fig. 8. Cross section of the atrioventricular region at the level of the A-V node (*1*) and bundle of His (*2*). The myocardium around the bundle of His is the site of recent infarction. Verhoeff ×7.

per cent of the cases, and from the left circumflex coronary artery in 45 per cent. In this case the artery to the sinus node originated from the right main coronary artery, and the recent thrombosis was just beyond its origin, as Dr. Pick had predicted. This explains satisfactorily the A-V block. The sinus node was not dissected but presumably would have been found to be normal histologically.

As previously mentioned, tumor metastases were present throughout the pericardium, but the myocardium was not involved. The tumor cells had the morphologic features of a poorly differentiated



Fig. 9. Detail of Fig. 8 showing the A-V node. Note the [illegible]
Hematoxylin-eosin ×75

adenocarcinoma quite consistent with a primary carcinoma from the breast. The *tumor cells were associated with a marked* fibrous thickening of the pericardium which was particularly prominent around the first portion of the ascending aorta (Figs. 11*A* and 11*B*). Although the measurements do not show a significant narrowing of the orifice of the aorta, I wonder whether the ejection murmur that had been described could have been caused by some degree of constriction or rigidity of the aorta as a result of the very severe pericarditis with tumor at that level.

Tumor metastases were present in the pleura of both lungs as well as in the lymph nodes and parenchyma of the right lung near the main bronchus to the upper lobe. Careful study excluded the possibility that this might have represented a different *primary* carcinoma. Metastases were also present in the liver and in one of the adrenal glands.

In conclusion, this is a case of coronary heart disease. Occlusion of the anterior *descending coronary artery, apparently* in August 1965, resulted in an infarction of the anterolateral wall of the left ventricle which was complicated by the formation of an aneurysm and mural thrombosis. At autopsy this infarct was obviously several months old. A very recent thrombosis of the right main coronary artery resulted in infarction of the posterior wall of the interventricular septum, including the bundle of His, as well as of the posterior wall of the right atrium. The A-V node appeared to be essentially normal. Unfortunately, no sections were obtained from the sinus node. There was a severe chronic adhesive pericarditis which was related to the older myocardial infarct as well as to the presence of tumor metastases from a primary carcinoma of the breast removed 14 years previously. *It is interest*ing to speculate that the richly vascularized



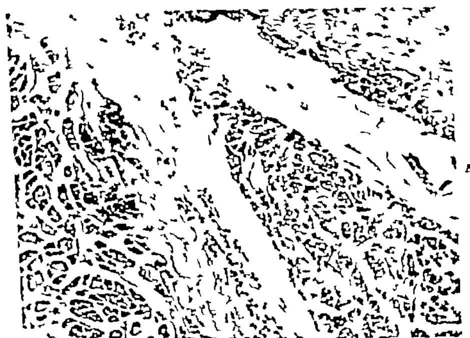


Fig. 10A. Detail of Fig. 8 showing the bundle of His. An infiltrate of hromic inflammatory cells ca be seen around and t a lesser extent ithin the bundle. Hematoxylin-eosin, ×75.

Fig. 10B. Detail of Fig. 10A. The muscle fibers of the bundle of His and those of the adjacent myocardium exhibit bnormal staining qualities consistent with arly necrosis. Small foci of calc fica ion re also present in the myocardium. Hematoxylin-eosin, ×195.

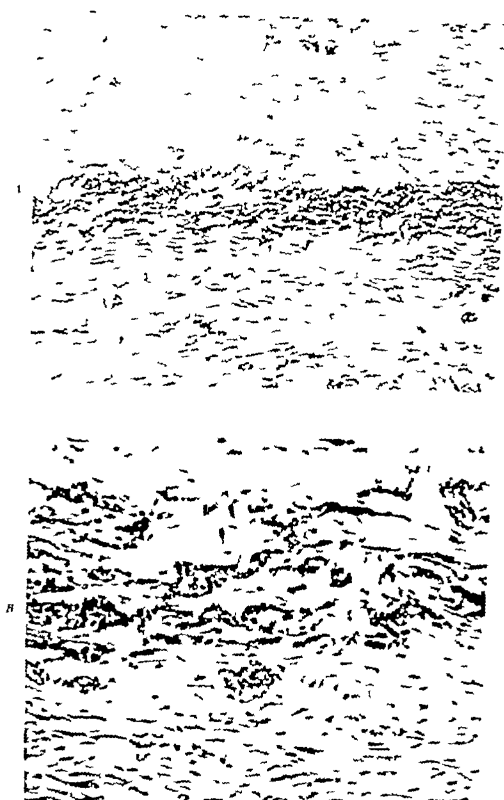


Fig. 11A. Numerous tumor cells are present between the wall of the ascending aorta (above) and the thick fibrotic pericardium (below). Hematoxylin-eosin, ×75.

Fig. 11B. Detail of Fig. 11A. The tumor cells are poorly differentiated and form irregular cords. Hematoxylin-eosin, ×220.

pericardium might have facilitated the development of metastases and that also might have provided a source of collateral circulation to the myocardium. The second coronary thrombosis, however, further interfered with the blood supply and the patient died in cardiac failure as evidenced by the pulmonary edema and bilateral hydrothorax. It was thought that the severe pericarditis was not constrictive in character although the ascending aorta was somewhat compressed. No definite evidence was found at autopsy to attribute the pericarditic process to a "Dressler phenomenon."

Anatomic diagnoses. (1) Severe coronary atherosclerosis with old occlusion of the anterior descending coronary artery and recent thrombosis of the right main coronary artery. (2) Old anterior wall infarction of the left ventricular myocardium with the formation of an aneurysm and mural thrombosis. (3) Recent posteroseptal infarction of the left ventricular myocardium and recent infarction of the right atrium. (4) Diffuse fibrous and fibrinous pericardial and pleuropericardial adhesions. (5) Metastases of breast carcinoma to pleura (bilateral), pericardium, left adrenal gland, right lung and hilar lymph nodes, and liver (status post left). (6) Cardiac hypertrophy, moderate (hypertension clinical). (7) Pulmonary edema. (8) Bilateral pleural effusion. (9) Masculinization.

RESIDENT. Were there any lung metastases?

DR. PIRANI. There were many small pleural metastases, as well as a larger area of involvement in the lymph nodes and pulmonary parenchyma around the bronchus to the right upper lobe.

RESIDENT. How about the lungs themselves?

DR. PIRANI. Just one or two very small nodules.

DR. GOLDEN. Any further questions?

DR. KATZ. I like your explanation of the ejection murmur, Dr. Pirani, because with the presence of pericardial thickening around the root of the aorta this region probably would not distend as much as the rest of the aorta during ejection, leading at that time to a relatively narrow part of the aorta. This might be the cause of a murmur. The other possibility is that the ventricular aneurysm itself might cause sufficient eddies to lead to a murmur during ejection.

DR. PICK. Since I have seen the instructive slides of Dr. Pirani two thoughts come to mind. The discrete histologic alterations in the specific A-V junctional tissues, with the A-V node almost entirely spared and the main lesion located in the common bundle, could very well provide an anatomic background for the sequential functional alterations reflected in the electrocardiograms by the variability in the ventricular rhythm. Thus in the intact meshwork of A-V nodal fibers a continuous activation front may have circulated at the assumed fast rate of 300 per minute. On the other hand, the lesion found distal to the node in the common bundle could account for the variable "exit block" of the rapid junctional impulses, many of which failed to reach the ventricles.

The other point that I should like to make is actually only an enlargement of Dr. Pirani's idea. There is one type of operation practiced for alleviation of anginal pain and that is dusting of the pericardium in order to stimulate vascularization and to revitalize viable myocardial tissue left within an infarct. In this instance nature may have acted in this manner, as suggested by the presence of widely patent vessels and islands of intact myocardial fibers within the fibrotic areas. Hence, the spread of the carcinoma to the pericardium may indeed have prolonged the survival time of the patient after such an extensive myocardial infarction.

DR. PIRANI. I agree with this. The pericardium was richly vascularized in part because of the irritating effect of tumor cells. The presence of the metastases may indeed have prolonged the life of this patient.

DR. KAPLAN. Dr. Pirani, at autopsy what is the appearance of the pericardium with the acute Dressler syndrome and after clinical control with steroid?

DR. PIRANI. This is a difficult question. I do not believe that one can make this diagnosis with any degree of certainty. Plasma cells should be present in greater number than might be expected in the usual pericarditis that follows myocardial infarction. Immunopathologic studies

might possibly help in thi respect but to the best of my knowledge no tudies of this type ha e been reported In thi p t tient tre tment witl rtic steroid m y ha e modified the h ra ter f the inflam matory ellul r infiltrat n the peri r dium in f ct enl f w pl sma ell were present im ng n m erou lymph c tes

FR TIES Are th re ins m re ques tion If n t we l md ljourned

REFERENCES

1 Dollinger M R La e I M J J M nd I nd re la t pos m rad t n fibr is f the m ter es C se f ur resd ll tre ed H I k d se w h l wer sophage l l ement J A M A 19 316 1966
2 Fresnler W M gement f per nd t ecti n dia t m and I t n Prog C rd s D 3 131 1960
3 St mler J I k R hat I N I k A Kapl n, B M Dickson D M l Cent D I ffect eness es rogen ther p d dual inf m in middle ge men J A M A 183 632 1963
4 J S P K R nd Ka I N Bench I om est erone nd h dro tisone on chol bemgenes levels on lem pr er therogen het Circ la ion Res 1 49 1963
5 I man R H H w ard, R J nd S erna, I N Effec f est lone sulfa t m d be h dr l diet pr ein on serum l pid nd liq prote nd their response t gonad l t read admin t t n, Circul t n 18 49 1958
6 Levigne J M re l d Ires, L T c ses f complet trom t l H k used by primary c rd c reom Arch M l Coeur 56 301 1963
7 H ller tei H h Ar l nd ect m w th d ng n tic lect ard gr phic find gs Am H J 36 122 1948
8 F sslher C h D e ses f the he rt ed 2 Phil delph 1956, W B Saunder C mp
9 Rosenl m I J hn ton, F D nd Alzamora, V V I er ent d placement of the RS-T segment an se f meta t tic tumor of the he t Am H r J 2 477 1944
10 R hbf ld, F I nd Z kin, R M Unus l lect rd gr phic es lence of meta t tic rd c umor resembl tru l nf rction, Am J C rdiol 10 52 1962
11 Ab m D f lel t, A Lura M H nd M ller A J Ventric l neurys m A re p pt r l b sed on tud d t h ner re repored se Circul ion 27 164 1963
12 Jen ings, R B Kaltenbach J P Sommers, H M B l C I nd Wartman, W B tudies f he d m rdial cells J mes, I N nd Ke es J W ed t rs The tiology f m rd l nfarc on, Bo on 1963 l tle B m A Compan h pter 12 pp 189-204
13 I M Wod J nd Erickson, I I A meth l f the his p hologic tud f he ent l node h d're nd l nches Arch I h 52 73 1951
14 I ml C nd hackler R Huma rd mdul n ure lesion Am J I h 36 311 1960
15 J mes, T N Anat m relat n hip f ns la the blood appl of the le nd tr ovent ri l node m he et r f m rd l nf rct n m J mes nd Keyes h pter 2 pp 311 33

Fundamentals of clinical cardiology

Fundamentals of cardiac pacing

Seymour Furman M.D.
Bronx N. Y.

The ability of muscle to respond to electrical stimulation has been known since Galvani's observation in 1 91. Little clinical use was made of this knowledge despite increasing awareness that cardiac muscle would respond to electrical stimulation and that spontaneous muscular activity was associated with significant electrical phenomena.

Aldini's attempt at cardiac stimulation in 1819, Duchenne's[2] effort in 18?0 at resuscitation of a patient with diphtheria and bradycardia, and Gould's [3] description of direct cardiac stimulation all stand out in an otherwise inactive period.

Study of electrical stimulation of the heart and its resulting contraction was carried out extensively during the third decade of the twentieth century by Wiggers,[7] who demonstrated many of the physiologic effects of such stimulation in the animal.

In 1931 Callaghan and Bigelow and Hopps and Bigelow stimulated the canine sinoatrial node with transvenously introduced unipolar and bipolar catheters during hypothermic cardiac arrest, to increase the rate of the heart with intact atrioventricular conduction. Although neither clinical follow-up nor long term studies were reported, catheter electrical stimulation of the atrium was demonstrated. In 193 Zoll demonstrated the clinical feasibility of closed-chest stimulation of the heart, using pulses of ? msec. duration and 75 to 150 volts in strength repeated 40 to 90 times per minute to produce cardiac systole.

This technique proved to be lifesaving and opened the era of widespread electrical stimulation of the heart of increasing durations with a continuous maximum of 7 days without respite[11] and with recovery. In 1957, spurred by the impetus of surgically produced A-V dissociation, Weirich and associates[12] demonstrated the clinical feasibility of direct electrical stimulation of the myocardium. An external pulse generator produced sustained repetitive ventricular contractions via wire leads exiting through the closed chest. The following year Furman and Robinson[13] demonstrated the short term feasibility of stimulation of the canine and human right ventricular endocardial surface by a transvenously introduced unipolar cardiac catheter. In 1959 Furman and Schwedel[1] reported the acute and chronic therapeutic application of transvenous cardiac stimulation in human beings. Prolonged stimulation with cardiac catheter and myocardial wire leads rapidly became feasible. An implanted system for continuous stimulation of the heart was reported by Glenn and associates[15] in 1959 utilizing radio-frequency induction of pacemaker stimul

From the Cardiothoracic Service, Surgical Division, Montefiore Hospital and Medical Center, Bronx, N. Y.
Supported in part by United States Public Health Service Grants No. HE09446-07 and HE09?46-01 (
Received for publication July 1968.
Address: Montefiore Hospital, Van Cortlandt Pavilion, Bronx, N. Y. 10467

into an implanted receiving unit with delivery of stimuli to the myocardium via two multi-strand stainless steel wires. Similar systems have been reported by Camilli and Meyrim[7] and associates and by Schuder.[1] Transmission of impulses across the intact skin demonstrated the feasibility of long-term intracorporeal stimulation without direct connection to an external stimulator.

Myocardial electrodes (in early unreliable components for reasons that were unclear at that time) of improved design became available (Hunter, Roth ... followed by the introduction by Chardack, Zoll and Kantrowitz and others of implanted myocardial electrodes coupled with self-contained implanted pulse generators containing the necessary circuit and mercury energy cells for the production of energy adequate to stimulate the heart for a period of several years.

Initially all pulse generators produced regularly timed stimuli yielding a fixed cardiac rate usually set between 60 and 70 beats per minute. In 1963 Nathan and associates[22] following a conceptual lead established earlier by Folkman and Watkins[23] and Stephenson and Kahn and associates[24] successfully bridged the A-V node producing a clinical pacemaker which stimulates the ventricle in response to atrial systole with a cardiac rate sensitive to those physiologic (and sometimes pathologic) stimuli which control atrial rate.

The units with myocardial electrodes of platinum iridium helical coil or modified stainless steel wire bore the brunt of clinical management of persons with symptomatic heart block for a number of years. However with increasing realization of the inability of both platinum iridium and stainless steel to sustain long-term cardiac stimulation because of metal fatigue produced by lead motion[26] as well as electrolytic reaction at the anode in all leads but those of pure noble metals, i.e. platinum,[27] with the high incidence of secondary thoracotomy for repair or replacement of leads, alternative procedures for long-term stimulation were sought. Data gathered by Escher and Schwedel[?] and Furman and associates,[29] using prolonged transvenous electrode catheter endocardial stimulation with an external pulse generator, and by Lagergren,[31] Lagergren[31] and Siddons[32] and associates using such stimulation with an implanted pulse generator demonstrated the efficacy and safety of transvenous endocardial stimulation for definitive management of complete atrioventricular dissociation.

Most recently the introduction of cardiac catheters specifically designed for long-term cardiac stimulation by the Elema Corporation, Medtronic, Inc., and Cordis Corporation have allowed progressively greater portion of asynchronous pacing to be performed by implanted pulse generators coupled with intravenous stimulation of the heart.

Research efforts have taken these directions: (1) Biologic power as a source of energy for the pacemaker has been investigated by Larsonnet[34] and Enger ... have rechargeable cells by Furman, Silver, and Bonnabeau;[36] these cells can be recycled through the intact skin and may be implanted directly upon the heart or placed subcutaneously for stimulation via myocardial or endocardial leads. (2) Newer modes of stimulation have been used to supplement the existing synchronous, asynchronous, and demand pacing modes. Paired, coupled, and atrial pacing all may have advantages in specific clinical instances. (3) Improved electrode systems have been developed with at least the hope of absolute reliability and prolonged durability.

Indication for cardiac pacing

I. Complete heart block with Stokes-Adams seizures. This is the classic indication for cardiac pacing and encompasses the bulk of patients paced. Some 85 per cent of all patients who have Stokes-Adams seizures do so on a background of complete heart block with periods of ventricular asystole.[41] The remainder develop circulatory arrest during bursts of ventricular tachycardia or fibrillation, usually but not invariably self-limited. Consistent stimulation of the ventricular myocardium, providing it with an adequate imposed rate and rhythm and ventricular blood flow and oxygenation, maintains a consistent cardiac output and prevents

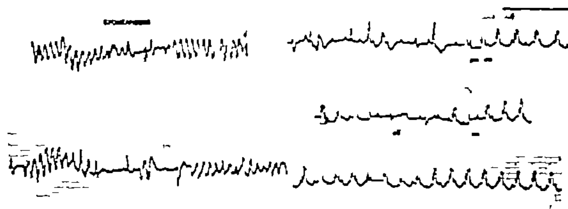


Fig 1 Ventricular tachycardia or fibrillation may produce circulatory arrest and when it occurs, asynchronous pacing is the mode of choice for control. The recurrence of tachycardia is controlled by asynchronous pacing and recurs with cessation of pacing

both asystolic and fibrillatory circulatory arrest. Indeed while drug therapy has been demonstrated to be of value in the control of asystole as a mechanism for Stokes-Adams seizures, it is less effective in control of the ventricular fibrillatory mechanism. During an episode of asystole, isoproterenol or epinephrine may aid in the restoration of idioventricular function during an episode of ventricular fibrillation or tachycardia, neither agent will be beneficial[a] and will tend to perpetuate the arrhythmia. Those sympathomimetic amines (isoproterenol and epinephrine) which increase cardiac rate by increasing myocardial irritability all exacerbate ventricular fibrillation or tachycardia, and in measured doses, their administration can be used as a diagnostic test when uncertainty about the mechanism for Stokes-Adams seizures exists. If during the course of complete heart block the administration of isoproterenol produces multifocal extrasystoles or continuous or short bursts of tachycardia then this mechanism is most likely to be operative and further sympathomimetic amine therapy is contraindicated[a] (Fig 1)

Another group of symptoms less dramatic but nevertheless significant are those associated with poor cerebral perfusion i.e. lethargy forgetfulness and other evidence of cerebral vascular insufficiency. Those symptoms may be markedly alleviated by the production of an adequate cardiac output, even in the absence of overt convulsive or syncopal episodes. Especially common are symptoms of light headedness and dizziness" which are unassociated with syncope but which may be considered to be "forme fruste syncopal episodes.

Pre renal azotemia as a result of slow cardiac rate and reduced cardiac output may occur in the absence of Stokes-Adams seizures. Such azotemia will respond to increases in cardiac rate and cardiac output with a lowering of blood urea nitrogen and a reduction in elevated levels of serum potassium.[a]

II Congestive heart failure This manifestation of complete heart block is frequently seen whether cerebral symptoms are or are not present. It was recognized early that when diuretics were ineffective in the control of congestive failure the institution of cardiac pacing alone produced prompt improvement, and that digitalis glycosides (which often produced asystole and were thus contraindicated during nonpacing management of complete heart block) could be administered with the customary indications. Increases in renal blood flow glomerular filtration rate and the excretion of sodium and chloride often accompanied the increase in cardiac rate to physiologic levels.[17] Increases in cardiac output have been regularly reported as a result of synchronous and asynchronous cardiac pacing

III Myocardial infarction. Complete heart block complicating acute myocardial infarction has long been recognized as a grave complication producing a fatality in the majority of reported cases. Since the availability of prolonged transvenous cardiac pacing instituted without major stress to the damaged myocardium it has become apparent that persons so afflicted can be salvaged during the acute episode, maintained until healing of the infarct and then subjected to procedures for prolonged pacing either transvenously or via direct myocardial implantation. Bruce and associates reported a mortality rate of 67 per cent in those patients not paced and 14 per cent in those patients undergoing transvenous pacing of the heart in the early postinfarction period as well as a 47 per cent rate of return from complete heart block to regular sinus rhythm during the course of healing of an acute myocardial infarction.

Treatment of arrhythmias other than classic atrioventricular dissociation has become possible either through utilization of short term pacing or permanent electrical stimulation of the heart[18] using the variety of stimulation available with asynchronous, synchronous, or demand pacemakers.

A. Sinus arrest associated with hyperkalemia with slow ventricular rate and/or multifocal premature ventricular contraction produces a picture similar to complete atrioventricular dissociation and three such instances have been treated. In all instances a reduction in the levels of serum potassium to normal resulted in a resumption of atrial activity, once with atrial fibrillation and twice to sinus rhythm, all with conducted ventricular activity and the loss of dependence upon electrical stimulation (Fig. 2).

B. Ventricular multifocal contractions may result from complete heart block and acute myocardial infarction. Such tachycardia or fibrillation may even occur in the absence of A-V block on a background of atrial fibrillation, flutter, or normal sinus rhythm. The imposition of a pacemaker rate more rapid than that of the dissociated myocardium will suppress the ectopic activity and produce regular activity.

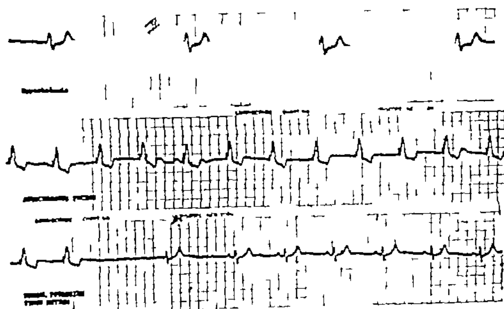


Fig. 2. Hyperkalemia (serum potassium of 7.4 mEq.) may produce sinus arrest and idioventricular rhythm and low ventricular rate. In this instance producing signs of intestinal ischemia. Asynchronous pacing increased intestinal blood flow with relief of symptoms and signs. Return of serum potassium to normal (4.4 mEq.) accompanied return of sinus activity and conduction.

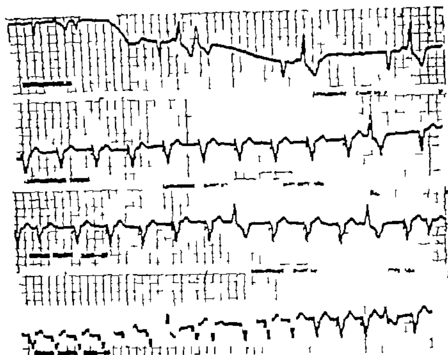


Fig. 3. The idioventricular rhythm characterized by multifocal coupled beats responds to either asynchronous or demand (standby) pacing. However, suppression of the multifocal activity is about equal for both modes. Increasing the rate of demand pacing does not increase the suppression of ectopic foci.

With correction of the underlying causes of the arrhythmia, pacing can be slowed or terminated[14] (Fig. 3).

C. Ventricular asystole, tachycardia, or fibrillation as an intercurrent event during sinus rhythm without any evidence of complete heart block may produce Stokes-Adams seizures. Suppression of this ectopic activity depends on the maintenance of cardiac rhythm even when conduction of an impulse fails. The presence of a consistent rhythm has prevented both asystole and the bursts of ectopic rhythms which produce circulatory standstill.

E. Digitalis toxicity may be characterized by prolonged periods of rapid multifocal ventricular activity. Such activity may appear to be prefibrillatory in nature despite the prolonged periods which the heart may tolerate. Again, suppression of multifocal activity depends on the imposition of a rate that is sufficiently rapid to override all ectopic foci. Use of asynchronous pacing is especially valuable here since the imposition of an overriding rate and rhythm is not dependent upon physiologic trigger mechanisms, either atrial or ventricular, but is controlled by the physician, with the ventricular rate set at any level adequate to produce a satisfactorily controlled ventricular rhythm.

In the illustrated case, severe digitoxin toxicity complicated by the erroneous administration of isoproterenol because of short periods of slow rate was converted from the ventricular tachycardia illustrated to stable, fixed pacing at 120 beats per minute. With the administration of potassium and no digitalis glycosides or isoproterenol, the underlying cardiac rhythm returned to atrial fibrillation with conducted beats; the rapid paced rate then was slowed and finally discontinued. Resumption of digitalization with digoxin was accomplished, and an adequately digitalized state was soon achieved without evidence of toxicity or multifocal ventricular activity (Fig. 4).

F. Intermittent heart block, perhaps more common than was previously thought, is especially vexing since the patient with intervals of complete heart block associ-

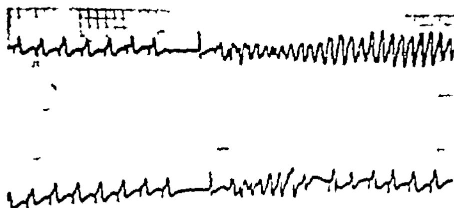


Fig. 4. [illegible] ventricular tachycardia [illegible] 120/ [illegible] the recurrence of atrial tachycardia [illegible] synchronous pacing.

ated with episodes of asystole or ventricular fibrillation. Assuming a customary normal sinus rhythm, which between episodes may appear to be completely unremarkable. Unless the electrocardiogram is observed during the brief period of atrioventricular dissociation, neither the heart block nor the mechanism for circulatory arrest will be adequately appreciated. Although asynchronous pacing will control these intermittent episodes, its use will be characterized by pacemaker-produced extrasystole and parasystole (when the heart is in sinus rhythm) with attendant awareness by the patient and discomfort, as well as the possibility, albeit remote, of pacemaker-induced ventricular fibrillation caused by stimulation of the heart during the vulnerable period of the cardiac cycle.[33] Synchronous pacing which completely suppresses normally conducted ventricular activity (when associated with a prolonged P-R interval)[33] or demand pacing in which pacemaker activity is suppressed by spontaneous ventricular activity is suitable for control of this variety of atrioventricular dissociation[34] (Fig. 5).

Cardiac output during pacing

In patients with complete heart block and normal atrial activity, either asynchronous or synchronous pacing may be used. Changes in cardiac output that occur during asynchronous pacing result from the ability of the heart to increase stroke volume,[35] whereas increases in cardiac output during synchronous pacing result from a combination of increased stroke volume, an increase in cardiac rate, and the contribution of the normally timed atrial systole to ventricular filling.[36]

An increase in cardiac rate from that commonly seen during atrioventricular dissociation, i.e., 30 to 40 beats per minute, to 60 to 80 beats per minute, pacemaker imposed, will at rest produce an increase in cardiac output of 50 to 80 per cent.[7] This is accompanied by the clinical observation of a reduction in congestive heart failure and diuresis without any other therapy. Further resting increases in asynchronous cardiac rate may produce momentary increases in cardiac output, although the output then descends (at the increased rate) to levels seen at slower rates. Indeed, some patients will have a critical rate well below the usual extremes of cardiac rate, above which cardiac output falls.[24]

Exercise at a fixed "normal" (70-80) cardiac rate usually results in an increase in stroke volume and a resultant increase in cardiac output. Some persons, however, respond with a broadening of the arteriovenous oxygen difference and no increase in cardiac output.[36] Both increases in

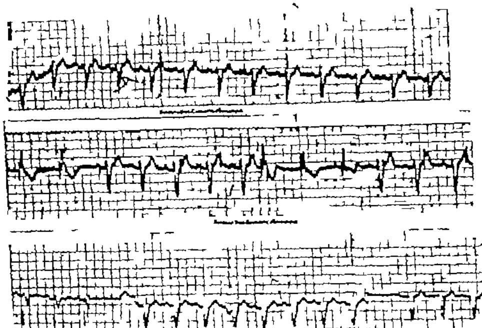


Fig. 5. Sinus rhythm with slightly prolonged P-R interval was characterized by occasional brief episodes of complete A-V dissociation, asystole, and circulatory arrest. Asynchronous pacing (*middle ECG*) produced competition between sinus rhythm and control of asystole (*beginning of ECG strip*). Synchronous pacing with an A-V delay of 0.16 second suppresses spontaneous sinus rhythm, eliminates competitive rhythms and produces consistent sinus rhythm.

stroke volume and cardiac output may be quite large and the clinical observation is that persons with fixed-rate pacemakers are capable of exertion without symptoms.

Synchronous pacing, i.e., with a proper A-V delay after atrial contraction, increases cardiac output even if the ventricular rate remains constant. Stroke volume increases up to 30 per cent, probably as a result of more efficient ventricular filling, although, since stroke volume decreases with increases in cardiac rate, this factor may be less significant for the person capable of both coordinated atrioventricular activity and increases in ventricular rate as a response to variations in atrial rate.[12]

Coordinated atrial and ventricular activity is especially important when insufficiency of the atrioventricular valves exists, since marked variation in phase between atrial contraction and ventricular systole produces enhanced mitral insufficiency and reduction of ejection via the aortic valve.[44]

Such studies of cardiac output are especially difficult to extrapolate to the individual patient unless he himself is studied because of the marked individual variation in myocardial capacity. Synchronous pacing may be of importance if the synchronous rate at which cardiac output falls does not lie within the normal rate response of the pacemaker. The application of synchronous pacing implies, as well, the presence of consistently stable atrial activity and, on a clinical level, the ability of the patient to withstand thoracotomy.

Modes of pacing

1. Asynchronous (fixed-rate) pacing imposed upon the heart by an electronic mechanism independent of body function is the basic mode of pacing, modified here indicated, and still used as the basis of therapy for the major indications for control of complete heart block. It is indicated for initial control of Stokes-Adams seizures caused by complete heart block, for sinus arrest, for multifocal ventricular contractions, and for the chronic

cerebral cardiac or renal failure associated with slow cardiac rates. It is not indicated for long term therapy of bursts of ventricular tachycardia or fibrillation imposed on underlying sinus rhythm.

Two varieties of asynchronous pacing are available: fixed and variable rate. The fixed rate unit is unable, once implanted, of varying its rate or of having its rate varied in any way in response to body requirements, i.e., exercise, increased metabolic state (fever, etc.), or to modify a change in underlying ventricular activity. Variable-rate pacers can be either adjusted via manipulation of a rate control with a triangular (Keith) needle percutaneously inserted into the unit or activated by external magnetic coupling.[1] Radio-frequency or inductively coupled pacer units are also of this basic mode but are readily amenable to variation in rate by manipulation of an external control. Despite variation in rate, these units are never synchronous with the atrium nor are they activated by any physiologic parameter. They are therefore, despite the flexibility inherent in variation in rate and control, asynchronous pacemakers (Fig. 6). Cardiac output, however, may vary significantly in response to bodily requirements even at a fixed rate. A sustained increase in cardiac output at asynchronous rates above 70 to 80 per minute while at rest has not been demonstrated. Exercise and increased metabolic state have also been demonstrated to increase stroke volume and cardiac output despite a fixed cardiac rate.

II. Synchronous pacing, activated by the atrial P wave, is the most physiologically responsive of the varieties available. In effect, it acts as a physiologic conduction system and differs only in that the point of origin of the left ventricular contraction is not from the conduction system itself, and that various electronic delay parameters do not allow it to mimic normal AV conduction completely. Cardiac rate, although not responsive to a change in the underlying ventricular activity, varies with bodily stimuli (the atrium) and increases or decreases with exercise and increased (or decreased) metabolic states.

The major problem inherent in synchronous pacing is the response of the pacer unit to pathologic as well as physiologic atrial activity. An increase in the formation of atrial impulses, such as atrial

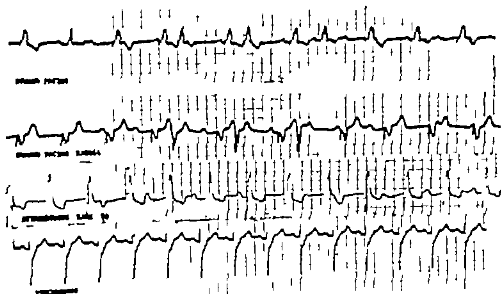


Fig. 6. Demand (standby) pacing allowed the appearance of occasional ectopic ventricular contractions. Asynchronous pacing at a slightly increased rate (70 beats per minute) suppressed most of this ectopic activity whereas synchronous pacing produced the most physiologic of all ventricular rhythms.

fibrillation or flutter will cause a ventricular response (even when this is undesirable) which is beyond external control. Despite the electronic block mechanism for atrial tachycardia, a ventricular rate to the maximum response of the pacer unit is possible. Patients now managed with fixed-rate pacing, i.e., patients with complete heart block and chronic atrial fibrillation, flutter, or tachycardia, would present a greater problem if synchronous pacing were utilized. Those young persons who are capable of great effort must be careful lest emotion or exertion drive the normal minute atrial rate above the factory-set block, with sudden and symptomatic reduction in ventricular rate to one half (i.e., 130 to 65 beats per minute). Some elderly persons who will tolerate a slow fixed rate develop angina or a fall in cardiac output at rates above 60 to 0 per minute. Patients have been studied in whom an incipient pulmonary edema occurred at a cardiac rate between 90 and 100, within the usual physiologic rate and well within the response range of the synchronous pacemaker itself.

Although in the physiologic state synchronous atrioventricular activity is most desirable, persons with heart block are in a pathologic state, only part of which may be correctable with a pacemaker. Since this is so, careful evaluation of the beneficial and deleterious effects of a return of normal atrioventricular conduction is necessary before synchronous pacing is embarked upon. In those patients in whom cardiac normalcy may be approached, i.e., patients with postsurgical heart blocks, young patients with good myocardial function, and older patients capable of rapid (100 to 130 beats per minute) ventricular function and stable atrial activity, a synchronous pacemaker should be considered (Fig. 7).

A major consideration favoring synchronous pacing is the suppression of sinus rhythm when alternation of sinus rhythm and complete heart block, with asystole or tachycardia and Stokes-Adams seizures, occurs. The P-R interval of the Cordis Atricor is 0.16 second, well within the range of normal P-R intervals. Those patients who display sinus rhythm occasionally interrupted by complete heart block and asystole or tachycardia often but not invariably have longer P-R intervals. Thus, each atrial P wave will be followed by a pacemaker-induced ventricular contraction, with the normally conducted impulse falling into the ventricular absolute refractory period. Although this mechanism functions well at slower cardiac rates, an atrial rate producing an R-R interval shorter than the refractory period of the pacemaker, 0.44 second, forces the unit to synchronize to the R wave and not the P wave, with the resulting pacemaker stimuli falling 0.16 second from the beginning of the R wave.

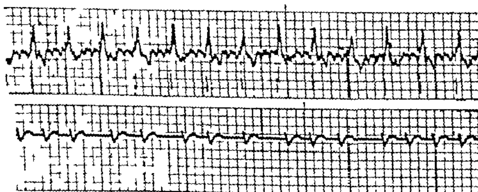
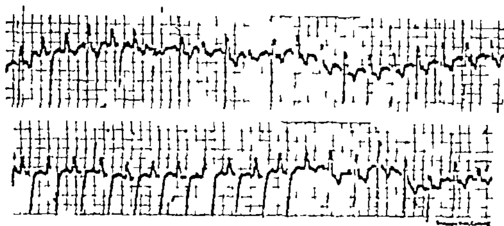


Fig. 7. Atrial flutter with asynchronous pacing results in regular controlled rate and rhythm. Atrial fibrillation and synchronous pacing with rapid and erratic ventricular response.



[illegible] synchronous [illegible] P-R longer than the pacer A-V delay produces typical [illegible] A-V [illegible] shortening of P-R [illegible] below the pacer A-V delay [illegible] the refractory period of the [illegible]

i.e., during the relative refractory period. With slowing of the atrial rate renewed synchronization to the P waves will result (Fig. 8).

This effect will be most prominent if the P-R interval is near that of the pacemaker A-V delay or if it shortens with an increase in atrial rate. Once the P-R interval reaches 0.16 second or less, normal A-V conduction will drive the ventricles with the pacemaker variably responding to the ventricular R wave or firing at *random portions of the cardiac cycle* with the atrial synchronous function inoperative (Fig. 9).

III. Demand pacing of the heart presents some of the features of asynchronous and of synchronous pacing.[29] Its strength and weakness are derived from these relationships. Demand pacing is asynchronous and fixed in rate. Yet function of the pacemaker is determined in part as a response to body activity, i.e., ventricular rhythm.

External demand pacer circuits have two basic variables, i.e., output of current into the electrode system and the basic rate at which the ventricles will be driven. Implanted demand systems are preset for output and rate, and neither variable exists. Any ventricular *activity in excess* of the preset rate blocks the pacemaker impulse and results in a lack of pacemaker activity. However, block of the demand pacer stimulus by ventricular activity is not a function of the total minute cardiac rate but rather of the sensing of a ventricular stimulus during the nonrefractory portion of the demand cycle. Thus, a low fixed spontaneous rate characterized by multifocal interpolated extrasystoles will suppress demand function if those extrasystoles fall at the proper time in the demand cycle. Such spontaneous activity may be sinus or ectopic, but in either event will block pacemaker activity. Although such demand pacing is highly desirable if patient demonstrates frequent change into and out of sinus rhythm, such pacing does not tend to suppress, but rather to accentuate ectopic ventricular arrhythmias, and an effective bigeminy or trigeminy may be produced in patients who have multifocal premature contractions. Bursts of ventricular tachycardia or fibrillation inactivate the pacemaker and therefore it does not provide a fixed active imposed rate which can be of great value in the control of this variety of arrhythmia.

A recently suggested standby system (Neville[41]) uses a pacemaker synchronized to the R wave at all times, with the P-R interval allowing the pacemaker stimulus to fall into the absolute refractory period of ventricular contraction. Such a system would not stimulate the ventricle at normal or rapid ventricular rates, but were the spontaneous ventricular rate *to fall*

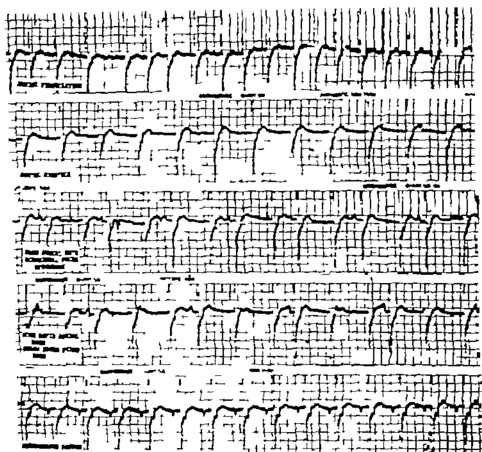


Fig 9 Synchronous pacing during ariety of trial activities Here the rapid irregular response to trial fibrillation which increases to the maximum rate of hich the pacemaker is capable (130 beats per minute). With trial asystole the pacer returns t its tomatic rate of 65 impulses per minute. Atrial activity substantially less than 65 beats per minute produces ynchronous response alternating with the pacer automatic rate More rapid trial rate till below 65 per minute, results in trial synchrony except when second P w e falls during the efractory period of the pacer after either synchronous or an tomatic impulse. An atrial rate abov the utomatic rate of the pacer yields consistent ynchrony

below 65 per minute (or any other pre determined figure) the pacemaker would revert to its ntrinsic asynchronous rate. Such a unit would be functional at all times and would therefore, provide an underlying pacemaker hythm for mini mization of multifocal ventricular contractions. One particular consideration of this system in the management of inter m ttent heart block over synchronous pacing is that the benefit of transvenous pacing may be obtained with this tech nique since only entricular myocardial or endocardial leads are utilized and no atrial pickup is necessary (Fig 10)

Also avoided are the effects of atrial instability since the major functional area of defect in complete heart block instability of ventricular contraction is controlled

Emergency therapy

Despite the variety of manifestations which atrioventricular dissociation presents, emergency pacemaker therapy is used in only a few For those situations in which no momentary threat to life exists, no emergency therapy is indicated and one many proceed to the management con idered to be subacute therapy

A patient seen initially t Stokes-Adams seiz and

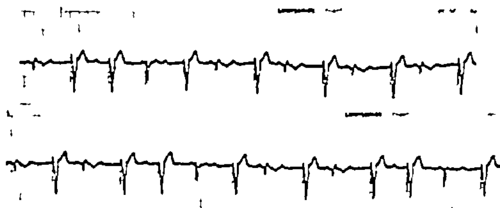


Fig. 11 Demand (standby) pacing stimulates the ventricles when spontaneous ventricular activity is delayed [illegible] and the pacer stimulus [illegible] When [illegible] occurs after a long delay (*lower middle and lower right*), [illegible] the pacer [illegible] suppresses the pacer impulse resulting in spontaneous QRS complex [illegible] superimposed pacer artifact

of asystole or with an irritable myocardium and episodes of ventricular tachycardia or fibrillation requires prompt therapy

1 *Asystole* An external pacemaker providing transcutaneous transmission of current across the closed chest is useful for resuscitation This the original pacemaker continues in active clinical use and provides a 2 msec shock of 50 to 150 volts across the closed chest Application is swift requires little skill and is basic for the emergency situation Because external pacing is painful and involves large amounts of electrical energy sedation is required and the skin must be observed carefully in order to avoid burns at the site of electrode placement.

Because of uncertainty of response and the burns and pain associated with external pacemaker therapy it is used only as an emergency measure and only as long as is required for placement of a transvenous pacemaker External pacing is not recommended for use during myocardial implantation of a pacemaker since the contracting musculature interferes with the surgical technique Its use therefore is brief

The parenteral administration of sympathomimetic amines especially isoproternol (Isuprel) is of special value in those patients who respond to the administration of them with an increase in cardiac rate without an increase in ventricular irritability and multifocal premature activity If the cardiac response is largely one of increased irritability and not of increased uniform rate or of slowing of the rate with conversion of a second-degree heart block to a third-degree block or of production of tachycardia then drug therapy is contraindicated [44]

B Ventricular tachycardia fibrillation The mechanism for circulatory arrest during Stokes-Adams seizures is ventricular fibrillation or tachycardia in some 10 to 15 per cent of instances Whenever this diagnosis is entertained or proved therapy is quite different from that for asystole Sympathomimetic amines are not only ineffective but tend to increase the irritability of an already irritable heart Thus, bursts of ventricular fibrillation that are self limited and not lethal may be converted into the lethal arrhythmia Pacing must be performed continuously and at a rate adequate to suppress most if not all ectopic activity This is painful and is difficult to accomplish with external pacing Defibrillation may be required frequently The administration of agents for the reduction of myocardial irritability may be equally problem provoking [a] Transvenous pacing of the right ventricle is suitable for prolonged control of such arrhythmias and can be instituted for as long or short a period as is indicated

Subacute therapy

Once the acute emergency has been controlled and the threat to life is past, the subacute phase of management is entered It is during this period that control of the heart rate and the production of an adequate cardiac output are utilized to bring a patient into optimal physical condition for the implantation of a "permanent pacing unit. During this time a firm diagnosis of the underlying state of the heart and conduction system is ascertained and chronic cerebral and renal improvement sought. This period may be brief or may be as long as is required to reach the desired therapeutic result. The implantation of a permanent pacemaker unit need never be undertaken as an emergency measure with consequent threat to life and the adequacy of the procedure. An even more significant reason for avoiding emergency implantation is that such a procedure does not add to the adequacy of pacing and may be performed before complete understanding of the disease process (often only possible with the passage of time) is available.

Thus, the time required for an evaluation of the patient may be brief if an individual who has well-documented permanent complete heart block controlled with medication suddenly deteriorates and may be prolonged for a previously well individual who is admitted with a myocardial infarction, complete heart block, and Stokes-Adams seizures. Here, subacute control suffices until the patient is able to tolerate the definitive therapeutic effort and the permanent state of A V conduction is determined

A Transvenous pacing of the right ventricular endocardial surface For both short term and long term pacing for early control of patients with complete heart block, and for prolonged control in some an electrode catheter (passed via the external jugular femoral or cephalic vein) may be utilized In skilled hands, control is rapidly achieved with a high degree of safety Thoracotomy is avoided comfort is maintained and carefully supervised indefinite maintenance of some patients on an ambulatory outpatient basis is possible. Neither short term nor long term resistance to stimulation has occurred when a free-floating catheter in the mid right ventricle has been used

Although transvenous stimulation is effective for any age group it is especially worth while when thoracotomy is contra indicated Although the catheter may be passed from any peripheral vein stability of position safety and consistency of pacing require that a site be selected from which there is little motion relative to the thorax. Passage from the cephalic vein at the delto-pectoral triangle the external jugular vein or the femoral vein is desirable from the basilic vein undesirable [17] The occurrence of malposition is usually related to a poor choice of vein or initial ventricular placement.

The external jugular route is suitable for prolonged pacing Even with an exteriorized pulse generator such an assembly is not incompatible with prolonged maintenance.[19] However that vein is ligated during placement and often cannot be reused For uses which are known to be brief i.e. for control during implantation of the pacer replacement or repair of a transvenous or myocardial pacer unit, or intraoperative control of an otherwise stable heart block percutaneous insertion of a No 5 or No 6 bipolar catheter into the femoral vein allows completely adequate cardiac control and safety for periods to 1 week.[15] During such short periods, the femoral vein does not thrombose and can be reused as frequently as is necessary

B Direct stimulation of the left ventricular myocardium by an electrode wire passed percutaneously through a needle into the chest provides a rapid approach to effective cardiac control. This technique is usable for short term applications and has been carried out with low morbidity [4]

Definitive therapy

Definitive therapy implies the implantation within the body of all or part of the functioning apparatus of a pacemaker Such implantation avoids the problem of infection of an external prosthesis traversing the open skin the vulnerability of externally placed components to patient abuse or accident, and the emotional problems associated with the wearing of

an external cardiac prosthesis. However, the disadvantages of such a system lie in the relative difficulty of service, whether for malfunction or exhaustion of the battery. Internally placed units are remote from external control, and this inaccessibility may complicate management when a major change in the well-being of the patient or atrioventricular conduction has occurred. All available implanted units allow passage of body ions and water through the silicone rubber and epoxy resin used to encase and protect the electronic components. Silicone rubber allows the passage of water vapor, and those epoxy resins now in use eventually reach equilibrium with the ambient moisture.[illegible] Since even the simplest circuits, such as those used in the receiving capsules of radio-frequency units, are vulnerable to such transmitted water vapor and ions, the problem of implanted components is not yet fully resolved.

Two different lead systems for definitive implantation are in favor, i.e., direct myocardial implantation and transvenous stimulation of the right ventricle. In addition to the stress of thoracotomy and the occasionally observed postpericardiotomy syndrome after implantation of the pacemaker, the lead system used are all non-noble metals (because of the inability of noble metals to withstand continued flexion). Anodal electrolysis thus must occur, and fracture of this lead is therefore a distinct possibility. Only Elgiloy,* which is more flex resistant than the other metals now in use and does not[illegible] undergo electrolytic attack as the cathode of a pacer lead system, appears to tolerate indefinite mechanical exposure as an electrode. However, Elgiloy can be used only in a unipolar system, since it is electrolyzed rapidly as a pacemaker anode.

The transvenous catheter leads are insulated throughout their course into the right ventricle with only the electrode exposed. Because the exposed electrode is unstressed, it may be made of pure platinum or Elgiloy rod. The insulated wire, unexposed to electrolytic activity, can thus be made of material selected for mechanical durability rather than resistance to electrolytic decomposition.

Two different modes of providing electrical energy are available. One is a totally implanted power source with primary mercury cells, which are the most reliable now available under low load conditions. The second is an externally powered radio-frequency transmitter, which, although wasteful of energy because of lossy transmission, nevertheless carries the pulse generator and its energy source externally, where battery replacement is readily possible.

Both situations provide advantages as well as disadvantages. There is little gainsaying the "out of sight, out of mind" advantage of the totally implanted units, although they suffer from the disadvantages of lack of accessibility should a major change occur in the state of well-being of the patient, and they do not allow major manipulation or replacement without an operative procedure with its attendant possibility of infection and operative morbidity.

The radio-frequency units, in theory, avoid this difficulty.[illegible] Yet these units customarily require a more complex external circuit and additional equipment, such as an antenna, connecting cable and attachments, all of which are vulnerable. In practice, these units have not yet achieved the reliability and stability inherent in the concept.

One advantage of the radio-frequency unit lies in the reduction in the number of internal (and vulnerable) and thus relatively unavailable components and the mathematical reduction in the possibility of malfunction of only a few components. The second is the ready control of rate if suppression of tachycardia or increase with activity is required.

Implantable pacemaker units are available in the asynchronous, synchronous, and recently demand modes. Since a fully reliable technique of transvenous synchronous pacing is not available, should it be selected for use, placement by means of thoracotomy is necessary.[illegible]

Management of the symptomatic patient with Stokes-Adams seizures presents the opportunity of substantial rehabilitation from uncontrolled idioventricular

*Elgin National Watch Company. Trademark for an alloy of cobalt, chromium, nickel, molybdenum, and manganese.

rhythm Simultaneously the variety of different therapeutic approaches relating to the lead systems, the power source and the modes of pacing allows control of almost all patients with whatever variety of block and in whatever state of systemic well being Correspondingly it is no longer wise for one variety of unit to be pressed into service for all patients. Most patients will certainly be well cared for with an implanted asynchronous pacemaker but for each patient the decision will remain whether this is to be a direct myocardial implant via thoracotomy or a transvenous implant and again whether radio-frequency or implanted energy source.

The indications for demand (standby) pacing are based on the underlying state of the conduction system and the idioventricular rhythm The indications for synchronous pacing are neither youth alone nor ability to withstand a thoracotomy but the desirability of a rapid ventricular rate the possibility of a return to sinus rhythm and if so the duration of the P R interval.

In any event there is little indication for precipitous definitive therapy with the inherent difficulty of modification The subacute stage of therapy can be skillfully managed for periods sufficiently protracted to allow observation of the natural course of the defect of A V conduction and selection of the pacemaker best suited for management

Both thoracotomy and transvenous placement of leads are possible The thoracotomy technique has been well described and is known to be reliable and effective However it places the leads, which are vulnerable because of electrolysis and motion fatigue away from ready accessibility Repair of malfunctioning major leads may require a secondary thoracotomy

The transvenous route is available for both asynchronous and demand pacers. Implantation can be performed as a subcutaneous procedure under local anesthesia and thus extends the procedure to persons unable to tolerate the challenge of thoracotomy Increased reliability of the electrode system because of reduction in electrolytic effect on the wire lead has also resulted since the conductive elements are insulated and the exposed terminals are unstressed and thus may be constructed of noble metal The use of a unipolar Elgiloy cathode and a large-area anode on the pulse generator reduces the effect of electrolysis upon the lead system

Placement of the catheter electrode into the apex of the right ventricle may be more difficult than placement of an electrode into the left ventricular myocardium until the requisite special skills are learned However once proficiency is acquired permanent transvenous pacing can be safely and surely accomplished

Pacemaker technology and the ability to influence cardiac rhythm has made marked advances in the recent past Control of cardiac rhythm with reliable implanted devices can now be readily obtained The major residual decisions involve rational choice of mode of pacing and route of application There are very few persons who now offer therapeutic problems of complete heart block which cannot be overcome with one or another technique of pacing

REFERENCES

1 Galvani, L. De viribus electricitatis in motu musculari commentarius, De Bononiensi Scientiarum et Artium Instit to Atque Academia Commentarii 7:363, 1791
2. Aldini, G. General views on the application of galvanism to medical purposes, London, 1819 J Callow
3. Duchenne, G B. De l'electrisation localisé, et de son application à la pathologique et à la therapeutique ed. 3, Paris, 1872, Baillière.
4 *Gould, 1929 Cited by Hyman.*
5. Hyman, A. S Resuscitation of the stopped heart by intracardial therapy Arch. Int. Med 50:283, 1932
6. Wiggers, C. J The muscular reactions of the mammalian ventricles to artificial surface stimuli, Am. J Physiol. 73:346, 1925
7 Wiggers, C. J Studies of ventricular fibrillation caused by electric shock, Am Heart J 5:351 1930.
8. Callaghan J C., and Bigelow W G. An electrical artificial pacemaker for standstill of the heart, Ann. Surg. 134:8, 1951
9 Hopps, J A and Bigelow W G Electrical treatment of cardiac arrest A cardiac stimulator-defibrillator Surgery 36:833, 1954
10. Zoll, P M Resuscitation of the heart in ventricular standstill by external electrical stimulation New England J Med 247 768, 1952
11 Douglas A H and Wagner W P Ventricular control by artificial pacemaker for seven days with recovery J.A M A. 153 1151 1954
12 Weirich, W Gott, V and Lillehei, P W Treatment of complete heart block by com

bined use of my c rdial electrode nd art ficial pacemaker Surg I rum 8:360 1957

13. F urm S nd Rol nson G Use of n intra cardiac pacem ker in c rrection of tot l hea t blk k Surg F rum 9:215 1958
14. Furm S and Sch edel, J B A t ardiac pacemaker for St kes-Adam seizu res, New England J Med 261:913 1959
15. Glenn, W W I M uro, A Longo, I Lav-etes, J H and MacKay F J Rem st tion lation of the heart l adio-frequency trans-miss m N England J Med. 261:918 1959
16. C milli, I I uzi, R a d Legnaudi, M Corriz me del blocco trovent ic lare com pleto sperimentale con pacem ker d elettrodo intramioc rdico Sett. Med. 17:217 1959
17. Abr m L D Hudson W A nd Light w od R A urgical pproach to th manage-ment of heart block using Inducti coupled artificial ardiac pacemaker Lancet 1 1372 1960
18. H ter S W nd Roth N A. The platform bipolar myoc rdial lectrode for prolonged tre tment of total heart block Journal Lancet 81 115 1961
19. Chardack W M Gage A A nd Gre t bat h, W A transistorized self-c ntained, implant ble pacemaker for the long term orrection of omplet heart block Surgery 48:643 1960
20. Zoll, P M F k H A Zarsky L R N Linenth l, A J nd Belgard A H Long term lectric tim lation of the heart for Stokes-Adam dise se A n Surg 154:330 1961
21. Ka trowitz A Cohen, R R illard, H Schmidt J nd Feldma D S The treat ment of cumplet heart block w th Implanted controllable pacemaker Surg Gynec & Obst. 115 115 1962.
22. Nathan, D A Center S, W C Y nd Keller W An implantable ynchronous pace-maker for the long term correction of complet heart block, Circulation 27:682, 1963
23. Folkman, M J nd W tkins, E.: A artificial conduction y tem for the management of experimental complete heart block, Surg Forum 8:331 1957
24. Stephenson, S. F Edwards, W H Jolly P C., nd Scott, H. W Phy iologic p w w cardiac stimulation, J Thoracic & Cardiovas. Surg 38:601 1959
25. Kahn, M Senderoff E Shapiro, J Bleifer S B., nd Grishman, A. Bridging of inter rupted A V conduction in experimental chronic complete heart block by electronic means, Am. Heart J 59:548, 1960.
26. Furman, S., Escher D J W Sch edel, J B., Solomon N and Rubinstein B. Implanted cardiac pacemakers—Motion factors producing lead breaks, Am J Surg 109 745 1965
27. Weinman, J and Mahler J The electrical properties of metal timulating electrodes, Bull. Res. Council Israel 10:3 1963.
28. Escher D J W Schwedel, J B., Schwartz, L. S. and Solomon, N Transvenous electrical stim lation of the heart. II Ann. New York Acad. Sc. 111:981 1964.
29. Furma S., Escher D J W Schwedel, J B., and Solomon N : Tra venous pacing A seven year review Am Heart J 71 408, 1966.
30. Lagergren, H., Zucker I R., and Asa, M M Preliminary i vestigation of the development of a permanent implantable pacemaker utilizing intracardiac bipolar electrode Clin. Res. 10 391 1962
31. Lagergren, H. Joha son, L., Landegren, J nd Edhag O One hundred cases of treat ment of Adams-Stokes syndrome with per manent i travenous pacemaker J Thoracic & Cardiov Surg 50 710, 1965
32. Siddons, H and D ies, J C.: A new tech-ique for i ternal cardiac pacing Lancet 2 1204 1963
33. Lagergren, H Johansson, L Schüller H Kugelberg J Bojs, G Alestig, K., Linder E Borst H G Schaudig A., Giebel, O Harm H Rodew H, G., nd Scheppokat, K. D 305 Cases of permanent intravenous pacemaker treatment for Adams Stokes yn-drome Surgery 59 191 1966
34. Chardack W M C ge A A., Federico, A J Schimert, G., and Gre tbatch, W : Five years clinic l experience with an implanted pace-m ker A appraisal, Surgery 58:915 1965.
35. Furman S., Escher D J W Solomon, N nd Sch edel, J B Impla ted transvenous pacemakers Eq ipment technique and clini cal perience A Surg 164 465, 1966.
36. Lagergren A The potentiality of biologic energy as power source for implantable pace-makers Ann. New York Acad. Sc. 111:915 1964
37. Fager C Kennedy J and Michel, A G: A ubminiature impla table self-powered car diac pacemaker Circu t design T Am Soc Art. Int. Organs 11 148, 1965
38. Furman, S Raddi, W Escher D J W Denize A., Schwedel, J B., and Hurwitt, E. S. Rechargeable pacemaker for direct myocardial implantation, Arch. Surg 91 796, 1965
39. Silver A. W Root G., Byron, F W., and Sandberg, H : Externally rechargeable cardiac pacemaker, Ann Thoracic Surg 1:380, 1965.
40. Bonnabeau, R., Ferlic, R. M nd Lillehei, C. W A new rechargeable epicardial cardiac pacemaker J Thoracic & Cardiovas. Surg 50:857 1965.
41. Stephenson, J E., J Reid, L. C., and Hinton, J W: Some common denominators in 1,200 cases of cardiac arrest Ann. Surg 137 731 1953.
42. Robbin, S. R., Goldfein, S., Schwartz, M J and Dack, S.: Adams-Stokes yndrome. The treatment of ventricular asystole ventricular tachycardia and ventricular fibrillation associ-ated with complete heart block, Am. J Med. 18:577 1955
43. Zoll, P M. Linenthal A. J Gibson, W Paul, M and Norman, L: I travenous drug therapy of Stokes-Adams disease Circulation 17 325 1958.
44. Schwedel, J B Furman, S., and Escher D. J W: Use of n intracardiac pacemaker in

the treatment of Stokes-Adams seizures, Prog Cardiovas. Dis. 3:170 1960.
45. Escher D J W Unpublished data.
46. Muller O F and Bellet, S Treatment of intractable heart failure in the presence of complete atrio-ventricular heart block by the use of the internal cardiac pacemaker Report of two cases, New England J Med. 265 768, 1961
47. Friedberg, C. K., Donoso, E., Stein, W G., Kahn, M and Litw L, R. The role of bradycardia in the retention of sodium and water in complete heart block with and without heart failure in human beings, Am. Heart J 69:293, 1965.
48. Courter S. R Moffat, J and Fowler N O Advanced trio-ventricular block in acute myocardial infarction Circulation 27 1034 1963.
49. Bruce, R. A Blackman, J R., Cobb, L. A., and Dodge, H T Treatment of asystole or heart block during acute myocardial infarction with electrode catheter pacing, Am Heart J 69:460, 1965.
50. Sowton, E., Leatham, A., and Carson, P The suppression of arrhythmias by artificial pacing, Lancet 2 1098, 1964.
51. Heiman, D F and Hel ig, J Suppression of ventricular arrhythmias by trans enous intracardia pacing J.A M A. 193 1150, 1966.
52. Dressler W Sterling, J and Rubin, R. Observations in patients with implanted cardiac pacemaker IV Repetitive responses to electrical stimuli, Am J Cardiol. 15:391 1965
53. Furman, S Cardiac pacing, Am. Heart J 70:830, 1965
54. Lemberg L Castellanos A and Berkovits, B. Pacing on demand A V block, J.A.M.A. 191 106, 1965
55. Johansson, B. W Complete heart block, Acta Med Scandina Suppl. 180 1966.
56. Samet, P Jacobs, W Bernstein, W H., and Shane, R Hemodynamic sequelae of atrioventricular pacing i complete heart block. Am J Cardiol. 11:594 1963.
57. Sowton, E. Hemodynamic studies in patients ith artificial pacemakers, Brit Heart J 26 737 1964
58. Judge, R Wilson, W and Siegel, J Hemodynamic studies i patients ith implanted cardiac pacemakers, New England J Med. 270 1391 1964.
59. Nathan, D A., Samet, P Center S., and Wu, C Y Long-term correction of complete heart block Clinical and physiologic tudies of new type of implantable synchronous pacer Prog Cardiovasc Dis. 6:538, 1964.
60. Samet, P Bernstein, W Nathan, D and Lopez, A. Atrial contribution to cardiac out put in complete heart block, Am. J Cardiol. 16 1 1965
61. Chardack, W H Heart block treated with an implantable cardiac pacemaker Past experience and current developments, Prog Cardiovas. Dis. 6:507 1964
62. Morris, J D Judge, R. D Leininger B. J and Voutz, F K. Clinical experience and problems encountered with an implantable pacemaker J Thoracic & Cardiovas. Surg 50:849 1965.
63. Leatham, A., nd Cook, P External electric stim lator for treatment of ventricular standstill, Lancet 271 1185, 1956.
64. Myers, G., Parsonnet, V., Keller J W Zucker I. R., and Gilbert, L. Permanent transvenous standby pacing I E.E.E. Convention Record 11:27 1966
65. Neville Joh F Personal communication.
66. Zoll, P M Linenthal, A. J Gibson W Pa L M. H and Norman, L. R. I travenous drug therapy of Stokes-Adams disease. Effects of sympathomimetic amines on entricular rhythmicity and trio-ventricular conduction, Circulation 1 :325 1958.
67. Escher D J W Furman, S., Solomon, N R bumstein, B., and Schwedel, J B Cine radiology in the evaluation of implanted and transvenous cardiac pacemakers, Fifth Rochester Symposium of Cine Radiology Rochester N Y March, 1966.
68. Solomon, N and Escher D J W A rapid method for pacemaker catheter electrode insertion, Am. Heart J 66 717 1963.
69. Thevenet, A., Hodges, P C., and Lillehei, C. W The use of a myocardial electrode inserted percutaneously for control of complet A V block by artificial pacemaker Dis. Chest 34:621 1958.
70. Greatbatch, W Chardack, W and Gage, A. Implantable cardiac pacemakers, I.E-E.E. Convention Record 11:.5, 1965
71. Braunwald, N S and Morrow A. G. Accelerated fatigue testing of vailable pacemaker electrodes and Elgiloy wire coils, Surgery 58:846, 1965
72. Glenn, W W L., Hageman J H. Mauro, A Eisenberg L., Flanigan, S and Harvard, M Electrical timulation of excitable tissue by radio-frequency transmission, Ann Surg 160 338, 1964
73. Carlens, E., Johansson, L., Karlof I and Lagergren, H. New method for atrial-triggered pacemaker treatment without thoracotomy J Thoracic & Cardiovas. Surg 50:229 1965
74. Schuder J C. Personal communication.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reappraisal of digitalis Part VI
Chemistry of commonly used cardiac glycosides

Alan F. Lyon, M.D.
Arthur C. DeGraff, M.D.
New York, N. Y.

The pure glycosides derived from digitalis leaf are responsible for the pharmacologic action of digitalis. Glycosides having cardiotonic properties have been isolated from many substances including squill, Convallaria, toad skin, etc. Over 400 cardiac glycosides are now available. Only a few of these, however, are available for clinical use.

The basic structure of all cardiac glycosides is the familiar cyclopentanoperhydrophenanthrene steroid ring coupled to an unsaturated lactone ring at the C_{17} position, as shown in Fig. 1. In the diagram, the lactone ring shown is the 5-membered one common to the glycosides of *Digitalis lanata*, *Digitalis purpurea*, and *Strophanthus gratus*, the natural plant sources of glycosides in wide clinical use in this country. Other glycosides isolated from squill (*Urginea maritima*) and from toad skins contain a 6-membered doubly unsaturated lactone ring.

When this basic molecule is coupled to a sugar at the C_3 position, it is known as a glycoside. When the sugar is removed and replaced by a hydroxyl group, it is known as an aglycone or genin. Genins, such as digitoxigenin and digoxigenin, can produce effects similar to those of the glycosides but are characterized by a distribution in different organs and a much briefer effect; they are of only academic interest. It is the sugar-containing glycosides that are clinically important. The sugar that is present in the pure glycosides digitoxin, gitoxin, and digoxin is identical in each. It is a desoxyhexose called *digitoxose* that is found nowhere else in nature. This unusual sugar is not, however, critical to the cardiac action of digitalis. Other glycosides contain more common sugars at the C_3 position. The sugar in the Strophanthus glycoside ouabain is rhamnose.

In addition to the lactone ring at C_{17} and the sugar at C_3, the glycosides contain varying substitutions at six positions of the steroid nucleus. These are listed in Table I.

Since the substitutions at C_{13} and C_{14} are the same in all, they differ in only four positions. Digoxin and gitoxin differ from digitoxin in that they each have one additional hydroxyl group. The conversion of a considerable amount of digitoxin to digoxin in the body is, therefore, quite understandable. The small differences that do exist are of great importance in the metabolism of these glycosides. The extra hydroxyl group of digoxin makes it more polar than digitoxin. Ouabain, having both an aldehyde group and extra hy-

Received for publication Nov. 18, 1966.

*Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N. Y.
**Professor of Therapeutics, New York University College of Medicine, and Consultant in Cardiology, Veterans Administration Hospital, Bronx, N. Y.

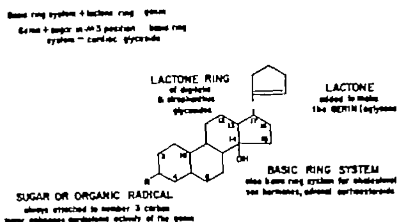


Fig. 1 Basic chemical structure of cardiac glycosides. (From Sperber R. J. Fisch, S., and DeGraff A. C. Some aspects of the clinical pharmacology of digitalis, Progress in Cardiovascular Diseases 3:299-303 1961 by permission.)

droxyl group is even more polar and soluble in water

The characteristic features of the cardiac genins as emphasized by Hoch are (1) Presence of an alpha beta unsaturated lactone ring (5- or 6-membered) attached to C and having a beta orientation (2) Presence of a beta-oriented hydroxyl group at C (3) A cis fusion of the C and D rings at C_1 and C (whereas other types of natural steroids usually show transorientation) (4) The attachment at C of one or more molecules of various sugars, including the rare type of desoxy hexomethyloses.

The commonly used glycosides digitoxin digoxin acetyl digitoxin lanatoside C and ouabain are available in reasonably pure form. Gitalin is a mixture of several water-soluble glycosides. Gitoxin which is present in both *Digitalis purpurea* and *Digitalis lanata* is not available for clinical use because of its relative insolubility

A classification of cardiac glycosides is somewhat complicated by a separate name for the precursor or natural glycoside *Digitalis lanata* for example yields three natural glycosides, which are called *lanatosides A B* and *C* With further hydrolysis an acetyl group and glucose are removed and the lanatosides are converted to digitoxin gitoxin and digoxin respectively Only lanatoside C of these three precursor glycosides is used alone clinically In addition an intermediate form of lanatoside C in which the acetyl but not the glucose group is removed is widely used for intravenous digitalization. It is called *deslanoside* (Cediland) Except for its greater solubility in water it is much more like lanatoside C than the digoxin that would be produced by further hydrolysis. Another intermediate glycoside of *Digitalis lanata* that is used clinically is acetyl digitoxin which is produced by the hydrolysis of the glucose but not the acetyl group from lanatoside A. Similarly there are two precursor glycosides of *Digitalis purpurea* which yield glucose and the pure glycosides digitoxin and gitoxin. They differ from lanatoside A and B only in the absence of acetyl groups. They are not used clinically Purification of *Digitalis purpurea* also yields gitalin which for some time was considered to be a third pure glycoside but is now known to be an amorphous mixture containing several glycosides.

Digitalis purpurea is still the source of most of the crude preparations of digitalis.

Table I

	Digitoxin	*Gitoxin*	*Digoxin*	*Ouabain*
C	—	—	—	OH
C_{10}	CH	CH	CH	CHO
C_{12}	—	—	OH	—
C_{13}	CH	CH	CH	CH
C_{14}	OH	OH	OH	OH
C_{16}	—	OH	—	—

Preparations of digitalis

1. POWDERED DIGITALIS, U.S.P. This is a crude extract of *Digitalis purpurea* assayed against reference standard in the pigeon heart so that 0.1 Gm. equals 1 U.S.P. unit. This is available as the powder, as tablets, as capsules of 0.05 or 0.1 Gm., or as suppositories.

2. DIGITALIS TINCTURE, N.F. This liquid form of crude digitalis was once popular but is now little used. One milliliter is equal to 1 U.S.P. unit.

3-4. DIGALEN AND DIGIFOLIN. These are partially purified preparations of *Digitalis purpurea*. Both are prepared for intravenous use in sterile solutions containing 0.5 U.S.P. unit per milliliter, as solutions for oral use containing 1.0 U.S.P. unit per milliliter, and in tablets also standardized in U.S.P. units.

5. GITALIN. This is marketed as 0.5 mg. scored tablets. Since this is a purified mixture rather than a pure glycoside, this weight standardization must be checked against a standard U.S.P. bioassay.

6. DIGITOXIN, U.S.P. Although the pure crystalline glycoside can be produced, U.S.P. standards allow a small amount of impurities to be present in commercial tablets. *It is standardized by weight and* is available in 0.1 mg. and 0. mg. tablets, as a powder, and in capsules.

7. DIGITOXIN INJECTION, U.S.P. The very poorly water-soluble digitoxin is dissolved in a sterile solution containing 40 to 50 per cent alcohol. It contains 0.2 mg. per *milliliter* and can be used only intravenously.

8. DIGOXIN, U.S.P. The pure glycoside is standardized by weight rather than bioassay. It is available as 0.25-mg. and 0.5 mg. tablets and as a pediatric elixir containing 0.05 mg. per milliliter.

9. DIGOXIN INJECTION, U.S.P. This poorly water-soluble glycoside is stabilized in a vehicle composed of 40 per cent propylene glycol, 10 per cent alcohol, and other constituents and can be used *undiluted* either intravenously or intramuscularly. It is available in 2-ml. ampules containing 0.25 mg. per milliliter.

10. LANATOSIDE C, U.S.P. This precursor glycoside is available only as *tablets* of 0.5 mg. It is standardized by bioassay on pigeons against lanatoside C.

11. DESLANOSIDE. This intermediate glycoside is assayed colorimetrically and standardized by weight. It is available in sterile solution in 10 per cent alcohol *in* 2 ml. and 4 ml. ampules containing 0.2 mg. per milliliter. It can be used intravenously or intramuscularly.

12. DIGILANID. This preparation is a mixture of the three purified precursor glycosides of *Digitalis lanata* (lanatosides A, B, and C) in the proportions in which they are present in the natural leaf. It is assayed by weight. It is available as 0.33-mg. tablets, as a solution containing 0.33 mg. per milliliter, as a rectal suppository containing 0.5 mg., and in sterile solution for intravenous use containing 0.2 mg. per milliliter.

13. ACETYL DIGITOXIN. This intermediate glycoside produced from lanatoside A is chemically pure and standardized by weight. It is available only in tablet form (tablets of 0.1 and 0.2 mg.).

14. OUABAIN INJECTION, U.S.P. (G-STROPHANTHIN). This pure glycoside derived from *Strophanthus gratus* is available in aqueous solution for intravenous use only. Concentrations of 0.25 and 0.5 mg. per *milliliter are available. Even though it is* a pure glycoside, it is standardized by a bioassay against standard ouabain.

There are other preparations which are little used today. These include strophanthin, N.F. (a glycoside from *Strophanthus kombe*) and scillaren, scillaren B, and urginin, which are derivatives of squill (*Urginea maritima*). A pure glycoside of the squill group called *proscillaridin* is presently the subject of clinical investigation.

In recent decades there has been a marked decrease in the use of the partially purified galenical digitalis preparations that are standardized by bioassay and an increase in the use of crystalline pure glycosides that are standardized by weight. *Although there are many* physicians who are quite adept in the use of digitalis leaf and see no reason to change, problems do exist in the bioassay that make for variability from lot to lot.

The bioassay of these products even

those intended for oral use is by parenteral injection into the pigeon. The bioassay of digitalis leaf is compared to the U.S.P. reference standard. However, variations in proportional content of the glycosides may cause variations in clinical response which would not be detected in the bioassay. For instance, a larger percentage of digitoxin in a digitalis leaf could cause the preparation to be more potent than would be indicated by the bioassay. This is because the bioassay is completed in a period before the maximum effect of digitoxin is attained. Thus, the bioassay is not a guarantee of clinical potency. Furthermore, the standardization by bioassay must be rather broad and allow for considerable actual variation. Therefore, it is our opinion that there is no reason for physicians beginning to use digitalis to use any but the purified glycosides.

REFERENCES

1. Hoch, J. H.: Structural features of cardiac glycosides and genins, Charleston, 1961, University of South Carolina Press.
2. Rafhlein, E., and Bocher, R.: Pharmacology of cardiac glycosides, in Luisada, A. A., editor: Cardiology: An encyclopedia of the cardiovascular system, Vol. V, Part 21, p. 133, New York, 1961, Blakiston-McGraw Hill.
3. Okita, G.: Pharmacology of digitalis, Pediat. Clin. North America 11:229, 1964.

Annotations

The heart in hyperthyroidism

Ca dia output nd rate The ha ges n cardiac funct on wh h ccur hyperth roid sm tachy rdia nd sed cardiac utput w th normal or ncre sed trok dume[1] resemble the effect f mpa hetic tim lation f the he rt To determ ne whether ncre sed sympathetic activ t pla ng tic t part in producing these irculat ry hanges ma workers ha tudied the effect f drugs h h interfere w th the these t rage or rele se of techolam nes wh h bl k mpa thetic recept rs Reserp ne nd lph -methyldopa were found to red the tach rdia nd, i more recent tud guaneth line w shown to reduce b th the tach ardia nd high cardia t put Beta mpathe bl kade with pronethalol wa reported by Wilson nd associates t ha no effect on the heart rat r output but How tt nd Rowlands f und that beta l lockade ith propranolol con stently reduced the heart rate of *hyperthyroid patient with sin hythm or trial* fibrillat on and reduced the cardiac output in 16 f the 18 patient wh were tudied The lack of response t pronethalol t the tudy f W lson nd workates may hav been due t the relatively maller dose of pronethalol that they sed

Thus number of drugs with different modes f act on but ha ing in common their bil'ty t diminish sympathetic activity reduce the he rt rate nd output Since the effect of propranolol on the heart rat in normal rest ng subject is slight and since it is generally accepted that there is nor mally little or no sympathetic activ ty t rest It is probable that the high rat nd output of hyper *thyroidism are t some extent produced by sympa* thetic activity

The tachycardia cannot exclusiv ly result from sympathetic timulation, ince complete beta blockade with propranolol does not reduce the heart rate t *normal levels. It is likely that the increase* in heart rat is partly due t the direct effect of thyroxine on the heart since it ha been show experimentally[1 14] that thyroxine has positiv chronotropic action on cardiac muscle Another factor may be diminished agal tone

Not all workers accept that the changes in cardiac function are mediated through the sympa thetic system. Tw recent observations from this laboratory raise possible doubt that the effects of propranolol in hyperthyroidism are purely those of beta bl kade: (i) the heart rat and cardiac output in resting myxedematous patients may be appreciably lowered by propranolol, and *(ii)* the *heart rate* and cardiac output in hyperthyroidism be reduced by the dextro-isomer of propranolol (wh h is lai med to ha ery l ttle beta blocking act ity), lthough the effect are les tha those pro luced by the racemic f rm

Myoc rdial contractility Ch nges in myocardial cont act lity hyperthyroid m are more difficult to measure than anat ons in heart rate nd output. The only accou t of left heart tudies i hyper th ro lism ha recently been published by Japanese w kers thers ha used indirect means of assess ng ontract l t from ar ri l pulse traces or l achial int rterial[1] or centr l rtic pressure recording These tudies ha hown diminished y tolic jection times, [1 21] incre sed ystolic ejection, [21 22] nd circumferential bort ing rates, nd high lues for aortic dp dt Pressure time per minute[1] (measure of tension time index) and left ventricular work [21] were increased It is likely theref re that there is increased myocardial con *tract lity The part played by incre sed sympa* thetic activity nd thyroxine in augmenting myo ardial contractil'ty are difficult t ssess but the increased heart r t nd enou return will ach ugment contractility by a utoregulatory mechanism independent of hormonal or nervous factors Propr nolol does reduce y tolic ejection rate[1] and aortic dp/dt but lthough these observ tions indicat reduction i contractility this could till be lue primarily t the associated f ll in heart rat rather tha to a dimi ished sympathetic inotropic effect.

Per pheral rculatory ha ges I contrast to the cardiac changes the changes in the peripheral circulation are not those expected from mpa thetic tim lation Blood flow in the limbs is in creased and the warm moist skin is associated ith dilatation of skin arterioles and the opening up of cutaneous capillaries [14 19] The total systemic arterial *resistance is reduced*, and the circulating blood olume is increased.[13] The net effect of these changes has been likened t that of large arteriovenous fistula.[14]

It has been suggested[7] that the impairment of *oxygen utilization in hyperthyroidism* leads to the accumulation of metabolites nd consequent vascu lar dilation. A increased production of heat from increased metabolism probably causes dilation of cutaneou vessels[14] as part of the temperature-regulating mechanism.

Whatever their mode of production, these pe ripheral changes would be expected to give rise to both autoregulatory and autonomically induced changes in cardiac f nction.

Therapeutic implications Drugs which diminish sympathetic activity may have some part to play in the management of thyrotoxicosis as a temporary measure until the disease is cured. Palpitation can be disturbing symptom, particularly in patients with atrial fibrillation and propranolol, guanethidine[19,20] and reserpine[4] have all been shown to relieve this symptom. Reduction in tachycardia may be particularly valuable in patients with associated mitral stenosis. Left ventricular work and tension time index are reduced by propranolol and by guanethidine so that these drugs reduce the work load and oxygen demand of the heart such action might be beneficial to patients with associated heart disease.

Both of these drugs, however reduce cardiac output without affecting total body oxygen consumption,[3,4] and the total arteriovenous oxygen difference must be increased. There are few observations on the nature or extent of the changes induced in the regional circulations or on any consequent disturbances of function. It has been shown that splanchnic blood flow may be insufficient to meet oxygen demand in thyrotoxicosis,[21] and that guanethidine reduces the fraction of systemic blood flow perfusing the splanchnic bed in hypertensive subjects[22] on the basis of these observations, Goldstein and Killip[2] suggested that, in hyperthyroidism, guanethidine may reduce blood flow to certain vascular beds out of proportion to the oxygen demand. A similar action may occur with propranolol but, since this drug has more specific cardiac action and less effect on peripheral vascular muscle it may be preferable to guanethidine. Even so, propranolol, as well as guanethidine should be used with caution in hyperthyroidism until the details of its action on the heart and regional circulations in this condition are more completely understood.

Geoffrey Howitt M.D M.R.C.P M.R.C.P.E.
Derek J Rowlands B.Sc M.B Ch.B M.R.C.P
University Department of Cardiology
Manchester Royal Infirmary
Manchester England

REFERENCES

1. Wade O L and Bishop J M Cardiac output and regional blood flow. Oxford, 1962, Blackwell, p. 193
2. Goldstein, S and Killip, T Catecholamine depletion in thyrotoxicosis, Circulation 31:219 1965
3. Howitt, G and Rowlands, D J Beta sympathetic blockade in hyperthyroidism, Lancet 1:628, 1966
4. Canary J J Schaaf, M Duffy B J and Kyle L. H Effects of oral and intramuscular administration of reserpine in thyrotoxicosis New England J Med. 257:435, 1957
5. Groot W J de, Leonard, J J Hyman, W I Johnson, J E., and Warren, J V The importance of autonomic integrity in maintaining the hyperkinetic circulatory dynamics of human hyperthyroidism, J Clin. Invest. 40 1033 1961
6. Theilen, E. O Wilson, W R., and Tutunji, F J The acute hemodynamic effects of alpha-methyldopa in thyrotoxic patients and normal subjects, Metabolism 12:615 1963.
7. Wilson, W R., Theilen, E. O and Fletcher F W Pharmacodynamic effects of beta-adrenergic blockade in patients with hyperthyroidism J Clin. Invest. 43 1697 1964
8. Yater W M The tachycardia, time factor survival period and seat of action of thyroxine in the perfused hearts of thyroxinized rabbits, Am. J Physiol. 98:338 1931
9. Markowitz C., and Yater W Response of explanted cardiac muscle to thyroxine, Am J Physiol. 100 162, 193..
10. Thier M D Gravenstein, J S and Hoffman, R. G. Thyroxin, reserpine, epinephrine and temperature on atrial rate, J Pharmacol & Exper Therap. 136 133, 1962.
11. Howitt, G Rowlands, D J Leung, D Y T and Logan, W F W E. Cardiac function in thyroid disease, In preparation.
12. Ueda, H., Sugishita Y Nakanishi, A Ito, I Yasuda, H., Sugiura, M Takabatake, Y Ueda, K., Koide, T and Ozeki, K. Clinical studies on the cardiac performance by means of transseptal left heart catheterization II Left ventricular function in high output heart disease, especially in hyperthyroidism, Jap Heart J 6:396 1965.
13. Sarnoff S J Gilmore J P and Wallace, A G The influence of autonomic nervous activity on the adaptive mechanisms in the heart, Randall, W C editor Nervous control of the heart, Baltimore 1965 Williams & Wilkins Co., p. 5.
14. Stewart, H. J and Evans, W F The peripheral blood flow in hyperthyroidism, Am. Heart J 20 715 1940.
15. Roberts, E and Griffith J Q A quantitative study of cutaneous capillaries in hyperthyroidism, Am. Heart J 13:598 1937
16. Graettinger J S Muenster J J Selverstone, L. A. and Campbell, J A A correlation of clinical and haemodynamic studies in patients with hyperthyroidism with and without congestive heart failure, J Clin Invest 38 1316 1959
17. Gibson, J G., and Harris A W Clinical studies on the blood volume V Hyperthyroidism and myxoedema, J Clin Invest 18:59 1939
18. Friedberg C. K. Diseases of the heart, ed 2, Philadelphia 1956, W B Saunders C p. 1001
19. Lee, W Y Bronsky D and Waldstein S S Studies of thyroid and sympathetic nervous system interrelationships II Effects of guanethidine on manifestation of hyperthyroidism, J Clin. Endocrinol 22:879 1962.
20. Waldstein, S. S West, G. H Lee W Y and Bronsky D Guanethidine in hyperthyroidism J.A.M A. 189:609 1964
21. Myers, J D Brannon, E S and Holland, B C A correlative study of the cardiac output and hepatic circulation in hyperthyroidism, J Clin Invest 29 1069 1950
22. Cohn, J N Liptak, T E and Freis, E. D Haemodynamic effects of guanethidine in man, Circulation Res. 12:298 1963.

Lumbar sympathectomy

In the 40 years since the introduction of lumbar sympathectomy for the treatment of peripheral arterial disease the operation has become an accepted procedure for the management of patients unsuitable for arterial reconstruction. Yet clinical studies reveal that although sympathectomy appears to benefit a proportion of patients with ischemic rest pain, considerable disagreement exists with regard to its value for the relief of intermittent claudication, chronic ischemic ulceration, or gangrene. Animal studies and clinical studies in normal subjects and in patients with arterial disease indicate that sympathectomy produces an initial marked increase in resting blood flow to the foot together with a considerably less marked increase in flow in the calf muscle, and that this initial increase is not sustained. Flow remains moderately elevated in the foot and returns to preoperative levels in the calf.

The symptoms of arterial insufficiency are usually not so much dependent on impairment of resting flow as on the inability to develop a hyperemic response. Indeed resting flows in the leg are usually normal in patients with arterial occlusion. Intermittent claudication results from diminished and delayed hyperemic response to exercise, allowing accumulation of undetermined metabolites above threshold levels sufficient to excite pain fibers. The mechanism of rest pain is less clear but it is postulated that the common episodic nocturnal rest pain results from an increase in skin metabolism from local heating that is greater than can be compensated for by a hyperemic response in the less ted foot. This flow accumulation of pain-producing metabolites. At times constant severe rest pain may result from irreversible ischemic neuritis. Finally persistence or progression of ischemic ulceration or gangrene also result from an inadequate local inflammatory hyperemic response.

Justification of the hemodynamic rationale for sympathectomy thus necessitates demonstration of not only an increase in resting blood flow to the particular area but also an increase in flow during hyperemia. Limitation of flow during hyperemia results from the resistance in collateral vessels which bypass the occlusion or resistance in precapillary vessels. Either resistance may in turn, be dependent on mechanical limitation of size as by disease or on persistent vasomotor tone. Presumably only the latter can be affected by sympathectomy.

A study was made of the changes occurring after lumbar sympathectomy in a group of 35 patients suffering from occlusive peripheral arterial disease. Measurements of various circulatory parameters were correlated with the symptoms and arteriographic localization of the disease. The clinical response to the operation was independently assessed several weeks after surgery. Bilateral sympathectomies were performed in 11 patients so that 46 extremities were considered; the indications for surgery and the principal sites of disease are shown in Tables I and II. Blood flows were measured by strain-gauge plethysmography in the calf, ankle, and mid-foot before and 10 to 14 days after sympathectomy. Resting flows were obtained under basal conditions with an environmental temperature of 22° 24°C; the peak flow and time of its occurrence in the calf were measured during reactive hyperemia after a 5-minute period of arterial occlusion. Similar measurements were obtained in the ankle and foot during reactive hyperemia with the leg warmed to a temperature of 42°C. The arterial pressures at the knee and ankle were measured with the plethysmograph, and the peripheral resistance during hyperemia was calculated from the ratio of the arterial pressure to the hyperemic flow.

The results are indicated in Tables I and II. In the total group of patients with intermittent claudication there was no appreciable change in the resting blood flow or in the peak flow or time of its development during reactive hyperemia in the calf nor was there change in the pressure measured distal to the occlusion. There was no appreciable difference in the values whether claudication was or was not associated with more severe symptoms of skin ischemia, whether the patient claimed clinical improvement, or whether the history was long or short. There was no relationship to arteriographic localization of the occlusion and runoff. The results suggested that peripheral resistance during hyperemia was higher in patients with associated rest pain and those who failed to show clinical improvement. It is thus considered that most patients who gained clinical improvement *did so by spontaneous gradual development of collateral vessels independent of the operation*, and that this was more likely to occur in patients with less generalized disease. It is possible that hemodynamic changes might have been manifest under different environmental conditions, particularly of temperature or with the patient in the erect posture. The possibility that the occasional apparently genuine relief of claudication from sympathectomy could result from division of afferent *pathways requires further reappraisal.*

On the other hand, both resting and hyperemic flow in the foot were markedly increased after sympathectomy even in the patients with severe ischemia. In spite of the fact that the peripheral resistance during hyperemia in the foot was higher *in these patients than in those without symptoms* of skin ischemia the corresponding changes in flow at the ankle were considerably less marked. Correlation with the arteriographic localization of the disease suggested that the more extensive the changes proximally the less apparent was the postoperative *increase in flow.* Eight of the 26 legs in which there were symptoms of skin ischemia failed to gain clinical improvement from sympathectomy and required

This work was supported by a Smith and Nephew Fellowship.

Table I

	Flow at H (ml./100 ml./min.)				Flow in foot (ml./100 ml./min.)				Peripheral resistance — Foot at peak flow (PRU)	
	Resting		Peak		Resting		Peak			
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
Symptoms										
Symptoms skin ischemia (20 legs)	0 8 ± 0 1	1 3 ± 0 1	3 2 ± 0 3	3 7 ± 0 5	0 8 ± 0 1	2 7 ± 0 3	3 4 ± 0 4	4 6 ± 0 7	29 5 ± 4	22 ± 2 5
Rest pain ulceration or gangrene (26 legs)	1 0 ± 0 1	1 7 ± 0 2	3 4 ± 0 5	3 1 ± 0 5	1 0 ± 0 1	2 2 ± 0 2	2 1 ± 0 4	3 5 ± 0 5	49 ± 7 5	38 ± 7
Clinical response										
Improved (18 legs)	1 0 ± 0 1	1 7 ± 0 2	4 0 ± 0 6	3 9 ± 0 7	1 2 ± 0 2	2 6 ± 0 3	3 1 ± 0 4	4 4 ± 0 6	32 5 ± 4	25 ± 4 3
Unchanged (8 legs)	1 2 ± 0 3	1 3 ± 0 3	1 8 ± 0 3	2 0 ± 0 4	0 6 ± 0 2	1 3 ± 0 4	1 0 ± 0 2	1 8 ± 0 5	80 5 ± 15	62 5 ± 15 5
Site of occlusion										
Aorto-iliac and femoropopliteal (9 legs)	0 8 ± 0 1	1 2 ± 0 5	2 3 ± 0 5	2 8 ± 0 5	0 8 ± 0 2	1 6 ± 0 3	2 9 ± 0 7	2 7 ± 0 8	46 5 ± 16	30 ± 10 5
Femoropopliteal only (28 legs)	1 0 ± 0 1	1 4 ± 0 1	3 2 ± 0 3	3 1 ± 0 2	0 9 ± 0 1	2 5 ± 0 1	2 8 ± 0 3	4 1 ± 0 4	40 ± 5 5	28 5 ± 5 5
Tibial vessels (9 legs)	0 7 ± 0 1	2 0 ± 0 3	4 7 ± 0 6	6 7 ± 0 9	0 9 ± 0 2	3 2 ± 0 4	3 4 ± 0 5	5 5 ± 1 1	54 5 ± 5 5	28 5 ± 7 5

Table II

	Resting flow in calf (ml./100 ml./min.)		Peak flow in calf (ml./100 ml./min.)		Time of peak flow (seconds)		Pressure at knee (mm. Hg)		Peripheral resistance — Calf at peak flow (PRU)	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
Symptoms										
Claudication only (20 legs)	1.5 ± 0.1	1.7 ± 0.1	7.0 ± 0.8	6.3 ± 0.8	30 ± 5	30 ± 5	105 ± 5	100 ± 5	17 ± 1.5	19.5 ± 2
Claudication and rest pain (20 legs)	1.5 ± 0.2	1.5 ± 0.2	4.8 ± 1.0	4.1 ± 0.7	50 ± 10	55 ± 5	85 ± 5	80 ± 5	21.5 ± 3	23 ± 3
Total group (40 legs)	1.5 ± 0.1	1.6 ± 0.1	5.8 ± 0.7	5.2 ± 0.6	40 ± 5	40 ± 5	95 ± 5	90 ± 5	21 ± 2	21 ± 2
Clinical response										
Improved (13 legs)	1.6 ± 0.1	1.8 ± 0.2	7.2 ± 1.5	6.5 ± 1.2	40 ± 10	40 ± 10	95 ± 10	100 ± 10	16.5 ± 1.5	17 ± 1.5
Unchanged (18 legs)	1.3 ± 0.1	1.3 ± 0.2	4.0 ± 0.5	3.3 ± 0.3	50 ± 10	55 ± 5	80 ± 10	70 ± 10	26.5 ± 4	26.5 ± 4.5
Site of occlusion										
Aorto-iliac and femoropopliteal (9 legs)	1.2 ± 0.1	1.6 ± 0.3	4.7 ± 0.9	3.8 ± 0.6	35 ± 5	60 ± 5	65 ± 5	75 ± 5	21.5 ± 4.5	26 ± 6
Femoropopliteal only (27 legs)	1.5 ± 0.1	1.6 ± 0.1	4.8 ± 0.4	4.4 ± 0.4	45 ± 10	40 ± 5	90 ± 10	85 ± 5	22 ± 2	21 ± 4.5
Tibial vessels (4 legs)	1.8 ± 0.5	1.5 ± 0.2	15.2 ± 3.1	13.7 ± 2.6	0	0	150 ± 10	145 ± 15	11.5 ± 4	13 ± 4

subsequent amputation or arterial reconstruction. The peripheral resistance in the foot was markedly higher in this group of patients which suggests that most failed t respond as result of severe generalized distal disease whereas f ilure to gain improvement in spit of increase i foot flow in 3 patients probably resulted from the presence of irreversible ischemic neuritis. I no case was stealing of flow from the foot t the kle observed, although the reverse phenomenon as commonly seen.

The combination of reactiv hyperemia and local heating of the foot ppeared t provide re liable means of prediction of the likely outcome of sympathectomy. In only one patient ho failed t gain clinical relief did the preoperati hyperemia flow slightly exceed 1.3 ml. per 100 ml. per minute, and in only one ho gained clinical relief was the flow slightly below this level. Similarly delay in development of the peak flow after elease of the arterial tourniquet of greater than 150 seconds was consistently associated with failure of clinical re sponse, although the mechanism of this delayed hyperemia is not clear.

K. A. Myers, M.B. B.S. (Melbourne), F.R.A.C.S.
Department of Surgery
St. M ry' Hospital
London, England

REFERENCES

1. Löfving, B., and Mellander, S.: Some aspects of the basal tone of the blood vessels, Acta physiol. Scandinav. 37: 134, 1956.
2. Barcroft, H.: Problems of ympathetic inner vation and denervation, Brit. M. Bull. 8:363, 1952.
3. Gillespie, J. A.: Late effects of lumbar ympathectomy on blood flow in the foot in obliterative vascular disease, Lancet 1:891, 1960.
4. Myers, K. A.: The use of strain gauge plethysmography in the investigation of peripheral arterial disease, Angiology 15:293, 1964.
5. Gairns, F. W., Garven, H. S. D., nd Smith, G.: The digital nerves and the nerve endings in progressive obliterative vascular disease of the leg, Scot. M. J. 5:382, 1960.
6. Myers, K. A., and Irvine, W. T.: An objective study of lumbar ympathectomy. I. I ter mittent claudication, Brit. M. J. 1:879, 1966.
7. Myers, K. A., and Irvine, W. T.: An objective study of lumbar sympathectomy. II. Skin ischemia, Brit. M. J. 1:943, 1966.

Primary prevention of coronary heart disease by diet

The morbidity nd mortality from coronary rtery disease poses an enormous public health problem in the United States especially for the middle-aged America male. Primary prevention in coronary artery disease is essential, despit the increased utilization of intensiv or coronary care units, because the incidence of sudden deaths in nd out of the hospital is still high as are deaths from acute myocardial infarction in the first da or fir t eeks of hospitalization.

The pathologic onset of coronary artery disease occurs many decades earlier than its clinical manifestation. Enos, Beyer nd Holmes has show that 13 per cent of young American soldiers killed in action in Korea showed plaques in the coronary arteries hich occluded half or more of the lumen. Strong and McGill report that in the age group 20 to 29 years the prev lence of coronary fibrous plaques as 15 per cent. At this ge Sch lling and associates has indicated that the serum cholesterol le l averages about 210 mg. per cent t age 1 h is 186 mg. per cent; t age 31 40 mg. per cent t ge 46 250 mg. per cent and by ge 58, erage maximum of 255 mg. per cent.

Some direction toward the primary prevention of coronary artery disease has resulted from the identification of the coronary artery disease risk factors, concept originated by the Framingham Study group[1] and amplified by others. Although these risks differ in relative significance such factors as obesity elev tion of serum cholesterol, hyper ension, smoking lack of activ y nd presence of diabetes mellitus ha been elaborated. Control of some of these factors by dietary means is possible od in ob both lowering of the total fat and change in the qualit of the f t intake together ith eight-reduction program when necessary. Many suggestions for such programs for the free living ambulatory person ha appeared in the literature [7] the best being that of the Diet nd Coronary Heart Disease Study Project of the Bureau of Nutrition of the Department of Health of the City of New York.

The diet of our subject ho were ithout clinical

evidence of coronary heart disease on entry t the Study w composed of approximately 18 per ent protei 42 per ent carbohydrate and 40 per t fat The division of t tal f t follow sat rated f tty cids, 46 per cent of total f t monounsaturated fatty cids 40 per cent nd poly nsat rated fatty ac ds 14 per ent The experimental (Prudent) diet eraged 19 per cent prot 48 per cent carbohydrate nd 33 per cent f t lories The distribution of the fatt acid i term of per cent of total f t as follow saturated f tt cids 33 per cent monounsatur ted f tty acid 33 per cent and poly nsat ted f tt acid 34 per cent Such diet (nd ght reduct on when necessary) has resulted gnific t decr se three of the aforementioned risk fact rs (obesit level of holesterol nd blo l pressure nd sig nifica t diminution in the nc lenc of linical coronary heart disease the periment l group when compared th the ontrol g oup fter 7 ears of observ tion The m k g h b t nd les l of activity of our exper ment l nd ontr l groups have not changed

I the experiment l roup of 814 active1 par ticipating men 40 t 5 ar of g there ere 339 confirmed new ron ry per 100,000 person years. I the control g of 463 men the com parable figure 980 per 100 000 person ears or almost three t mes ma ew even (These figures ho per 9 of observ tion) Criticism of these resul t se of the predom nant Jewish extraction of our observed groups seem t be arra ted so far world population tud ies of high and l w pr lence are of coronary rt ry disease are rel t f t l mat geograph or th origi nd so far as the t of p proximat l l per 100 new oronary event the control group compar ell th the national verage for this ge grou p

The Prudent Diet lowers serum trigl cerides[10] The alue however of the serum trigl ceride level rather tha the serum holesterol level as more important pred tor of coronary heart disease first proposed by Albri k nd M has not been sus sta tiated[10] L kewise the importance in the role of ingestion of carboh drates in he serum cho lesterol level as proposed b Yudkin[16] ha not been confirmed b others.[17,18] McGand nd as sociates[20] state that I term of practical ma ip ulations in American diets, t seems unlikely that alterations in the sources of dietary carbohydrates would be a usef l addition t modifications of dietary f ts in achiev ng blood cholesterol reduc tion Keys[21] ha proposed that the important saturated f tty acid hich account for elevation in th serum holesterol lev l is palmit acid and Stare, myristic acid. Nevertheless analyses of depot f t of the f tty acid of subjects on the Prudent Diet for periods of 1 through 4 ears indicate that the diet decreases both of these f tty acids i the depot f t, whereas it increases the level of linoleic acid.[22] The Prudent Diet is nutritionally sound even after 7 years of observ tion[10]

The nutritional adequacy of the Prudent Diet its acceptance by free-living ambulatory subjects, t capacity to lower serum cholesterol nd triglyceride levels, and, most importa t, its pparent influence on the ignificant reduction of new clinical coronary artery disease event make it, in our opinion an importa t public health modality for primary prevention of coronary heart disease

Seymour H. Rinzler M.D. F.A.C.P.
Morton Archer M.B.A. M.P.H.
George J. Christakis M.D. M.P.H.
Diet and Coronary Heart Disease Study Project
Bureau of Nutrition
Department of Health
New York City N. Y.

REFERENCES

1. Meltzer L. E. and Kitchell, J. R. Intensive care unit for patients with acute myocardial infarction Lancet 1 106 1965
2. Enos, W. F. Jr Beyer J. C. and Holmes, R. H. Pathogenesis of coronary disease in American soldiers killed in Korea, J.A.M.A. 158:912 1955
3. Strong J. P. and McGill H. C. Jr. The natural history of coronary atherosclerosis, Am. J. Path 40:37 1962.
4. Schilling F. J. et al. Studies of serum cholesterol i 4,244 men and women An epidemiologic and pathogenetic interpretation, Am. J. Public H lth 54 461 1964
5. Kannel, W. B. Dawber T. R. Kagan, A. Revotskie, N. and Stokes J. III Factors of risk the development of coronary heart disease Six year follow-up experience The Framingham Study Ann I t. Med. 55:33, 1961
6. Stamler J. et al. Coronary risk factors. Their impact and their therapy in the prevention of coronary heart disease M. Clin. North America 50:229 1966
7. Epstein F. H.: Epidemiology of coronary heart disease—A review J. Chron. Dis. 18 735, 1965
8. Page I. H. Green, J. G. nd Robertson, A. L. The physician incomplete guide t atherosclerosis, A I t Med 64 189 1966.
9. Doyle J. T. Etiology of coronary disease R sk factors influencing coronary disease Mod. Concepts Cardiova Dis 35:81 1966.
10. Chapman, J. M. nd Massey F. J. The interrelationship of serum cholesterol, hypertension, body weight and risk of coronary disease Result during the fir t ten-years Follow up i the Los Angeles study J. Chron. Dis. 1 :633, 1964
11. Kannel, W. B. Dawber T. R. Friedman, G. D. Glennon, W. E. and McNamara, P. M. Risk factors in coronary heart disease. An evaluation of several serum lipid as predictors of coronary heart disease. The Framingham Study Ann. I t. Med 61:888, 1964
12. Diet nd possible prevention of coronary theroma. A council statement, J.A.M.A. 194 1149 1965.
13. Central Committee for Medical and Community Program of the American Heart Association Dietary fat and it relation to heart

Address Kips Bay Health Center 411 East 69th St New York, N. Y. 10021

ttacks nd strokes, Circulation 23 133 1961
14 Stare F J N tritional suggestions for the primary prevention of coronary heart disease J Am Dietetic Assn. 18:88, 1966.
15 Keys, A Anderson J T and Grande F Serum cholesterol response to changes in the diet. IV Particular saturated fatty acids in the diet, Metabolism 14 776, 1965.
16. Dayton, S Pearce M L and Hiscock F Ca changes in the American diet prevent coronary heart disease? J Am. Dietetic Assn 46:20, 1965
17 alker W J Prevention of coronary heart disease Med. Arts nd Sc 18 130, 1964
18 Christakis, G., Rinzler S H, Archer M et al The Anti Coronary Club. A dietary pproach t the prevention of coronary heart disease A seven-year report, Am J Pub Health 56:299 1966
19 Toor M Katchalsky A Agmon J nd Allalouf D Atherosclerosis nd related factors in immigra ts to Israel Circulation 22:265 1960.
20. Christakis, G Rinzler S H Archer M and M slansky E Sum mary of the research ac ti ties of the Anti-Coronary Club, P b Health Rep. 81:64 1966.
21 Albrink, M J and Man, E B Serum triglycerides in coronary artery disease Arch I t. Med. 103:4 1959
22 Brown, D F Kinch S H and Doyle J T Serum triglycerides i health and in ischemic heart disease New England J Med. 273:947 1965
23. Yudkin J Dietary f t nd dietary sugar in relation t ischemic heart disease and diabetes, Lancet 2:4 1964
24 Yudkin, J nd Roddy J Levels of dietary ucrose in patients with occlusive atherosclerotic disease Lancet 2:6 1964
25 Hodges, R E and Krehl W A The role of carbohydrates in lipid metabolism, Am. J Clin. Nutrition 17:334 1965
26 McGandy R B Hegsted, D M M yers M L., and Stare, F J Dietary carbohydrate nd serum cholesterol levels in ma Am. J Clin. N trition 18:237 1966.
27 Christakis, G. J Rinzler S H Archer M Hashim S nd V Itallie T B Effect of serum cholesterol lowering diet on composition of depot fat in man, Am. J Clin N trition 16:243, 1965.
28. Christakis, G J Rinzler S. H Archer M H shim, S A., Hillman, R W and Van Itallie, T B Effect of cholesterol-lowering diet on the serum cholesterol, serum trigl cerides, serum vitamin A and E levels, and f tty acid composition of subcutaneous f t in man, Circulation 28 703, 1963.

Aneurysmal degeneration of arterial homografts

The fate of arterial homografts is of more tha historic interest since (1) there are many liv ng patients with f nctioning grafts, nd (2) arterial homografting is inherent in orga transplantation An appraisal of the 15-year clinical experience th rterial homografts is helpf l in planning f ture management of free nd pedicle arterial homografts.

Early complications of the use of homografts as arterial substit tes were leaking t the nastomoses with the formation of pseudoaneurysms and intestinal fist la f k rupture of the graft infec tion thrombosis, nd the formation of neurysms Lat complications ha been the development of therosclerotic hange thrombosis, and neurysmal dilatation. The threat of neurysmal hange with rupture or thrombosis of functioning grafts is presen ly of concern since the incidence in long-term impla ts has been found t be high

Aortic homografts ha beha ed differently as group th femoropopliteal homografts. The patency rate ha been much better nd the forma tion of neurysms has been less frequent in the former I one group of 160 successf l aortic homograft followed for long as 56 months only 2 neurysms ere reported nd they occurred in the femoral segment of the bifurcation grafts Of 71 successf l femoropopliteal homografts from the same series 12 had aneurysmal degeneration when followed 24 to 66 months. In another reported series of 55 aortic grafts followed 1 to 48 months 5 (9 1 per cent) dilated or became neurysmal, whereas in the same series of 77 liac grafts, followed 1 t 48 months 9 (11 7 per cent) became aneurysmal I 47 femoropopliteal grafts followed 1 to 56 months 14 (29 8 per cent) became aneurysmal Thus, aneurysmal degeneration has been much more common in medium-sized muscular arteries than in the aorta When the period of f llow-up has been extended t up to 10 ears, all patent femoropopliteal grafts hav eventually become aneurysmal

The reason for the divergence in beha ior of these grafts is perhaps related t their different structure. The media of the aorta is 70 to 80 per en elastin [12] whereas the femoropopliteal segmen has 1 to 3 per cent la tin in the media and 10 30 per cent elastin in the adventitia [14] The ell-documented

histologic hanges hich occur after rterial homografting onsist of death of the i tima th re placement by usually thick layer of hypocellul homogeneous hy linized- ppe ring tissue ha ing an endothelium l m ted t the end of the graft The smooth muscle cells of the media lying be t een the ela tic fibers degenerat nd the l ost tissue is compressed int dark-staining coarse band l ing l homogeneous pale-stain ng acellular stroma ha ing w y fibrill r structure There is ciable grow th of f brous tissu n nd ar ound th adventitia th the presenc of pill ries nd sociated hronic nflammat ry ell It ould ppear that the trength of the g aft resides in the elastic tissue nd n the fibrous prolifer t m s sociated th the ad entitia The th n ing nd d sruption f the l stic fiber ssociated ith g ft neur sm ha long been rec gnized. The relat l k of l st tissue in musculu arteri might predispose them t such d latation Histolog tudy f gr ft prior t use ha not allowed pre le ion f those gr ft prone t degener t on The use f fresh iably tored n non iably t ored gr ft terilized b sever l different method has not ltered the incidenc of degener tion

Three eur es luation of fibrocollagenous u t logous and homologous t be used to repl c the ne bdominal aort ha not res led eurysmal hange This does not indic t that lastic tissue necessary to support an rterial graft but ther that tructured fibrocollagen might be adequat substit t

I nce using arterial homogr ft should be fol low d t least arl Whe resection nd t l for neurysmal degener tion the entire graft should be emov ed or isola ed from the rterial tre m nd replaced th Dacron prosthesis the aortoiliac sit r by n t logous ein f t is in the femoropopliteal region

Imm nosuppressi therapy has been tilized experimentall ith l ttle or no effect iveness lter ng the degener t hanges i arterial homografts l contrast the ma renal arteries from homografted kidneys, treated ith sim l r egimen of imm nosuppression up t 1 year nd showing mild rejection hav hown less severe degenerati hanges tha the arterial graft This differenc may be related t more exact ng immunosuppressi regimen ith the renal graft or t better preserv tion of the sa sorum I the isolated arterial homograft the vasa asorum from two of three sources do not regenerat [19] Medial degeneration in the bsence f imm ne cells may be related t an imm nologic i terference ith re-establishment of the asa vasorum or t humoral antibody [20] Although the arterial homograft is probably eakl antigenic (as is the enous homograft) this does not seem t afford protection from degenerati hanges as evidenced by the trong tigenic timulus sociated w th renal grafting and the better preserv tion of the renal artery

Study of the intrarenal rteries from homografted canine kidneys showing variable degrees of rejection p to 2 years after grafting reveals severe changes.[21] Fibrinoid necrosis of arteriolar and rterial walls was found t be an earl lesion hereas fibrous intimal thick ing with some medi l necrosis and degeneration of the internal la tic l mina occurred i 64 per cent of tran plant urvi ing beyond 70 days.

Sev n human kidney homograft that failed 1 t 3 y ars ft grafting ha n t shown the form tion of en l arterial neurys m Nineteen human kidney homograft ha e show arterial lesions sim lar to those noted experiment ally [22] and in one there severe degenerat on of th renal artery I brinoid nec osis is f llowed by f brous changes n the media damage t the internal ela tic lamin nd prominent obl terativ fibrous intimal proli fer tion

It is noteworth that despit immunosuppres si therapy degener th hanges occur (1) iso l t d rt ial homogr ft nd t lesser degree in (2) renal rtery hom gr ft The renal rtery must la essel s that le th of the smooth m scle le onl small mou t of lastic tissue t maintain the tegrit f the essel.

Aneurysmal degener t on f the homografted renal artery ha not bee reported Immunosuppres sion adequat t protect the k dney may preserv the media f the artery nd render neurysmal hange ext emely lik l H pef lly this ill be the se bec use more org ns ll be tr spla ted the f ture nd their s lar pr l lem hould be observed f or this potential ompl t on.

Henri k B Barner M.D
Department of S rgery
St Louis U iversity
St Louis Mo.

J me l DeWeese M.D
Department of S rgery
U iver it of Rochester
Rochester N Y

REFERENCES

1 Barner H B DeWeese J A Dale W A and M hone E. B Aneur smal degeneration of femoropopl teal arterial homografts, J A M.A. 196:631 1966
2 Coleman, C C J Deterling R A J and P rshley M S. Some long term observations on aortic homografts, Surgery 37:64 1955.
3 Cra ford, F S DeBakey M E Morris G. C J and Garrett F E aluation of lat failures after econstructive operations for occlusive lesions of the aorta and iliac, femoral nd popliteal arteries, Surgery 4 79 1960.
4 DeBakey M E Creech, O J Cooley D A., and H lpert B Structural changes in human aortic homografts Study of 10 cases Arch. Surg 69:472 1954
5 DeWeese, J A., Terry R Barner H B and Rob, C. G. Autogenous venous femoropopliteal bypass graft, Surgery 59:28, 1966
6. DeWeese J A Woods, W D nd D le W A F lures of homografts as rterial replacement Surgery 46:565 1959
7 Haimovici, H and Maier N Experimental

Address Department of Surgery St. Louis University 1325 South Grand Blvd St. Louis, Mo 63104.

evaluation of arterial homograft. Wesolowski, S. A., and Dennis, C., editors: Fundamentals of vascular grafting, New York, 1963, McGraw-Hill Book Co., Inc., pp. 212-231.
8. Hawk, W. A., and Humphries, A. W.: Observations on arterial homografts, with special reference to pathologic changes: A preliminary report, Cleveland Clin. Quart. 24:26, 1957.
9. Jordan, G. L., Jr., DeBakey, M. E., Stump, M. M., and Halpert, B.: Lining of vascular homografts and prostheses, in Wesolowski and Dennis, pp. 175-190.
10. McCune, W. S., Thistlethwaite, J. R., Keshishian, J. M., and Blades, B.: Nutrition of blood vessel grafts: India ink injection study of their vascularization, Surg. Gynec. & Obst. 94:311, 1952.
11. Murray, J. E., Gleason, R., and Bartholomay, A.: Second report of registry in human kidney transplantation, Transplantation 2:660, 1964.
12. Porter, K. A.: Pathological changes in transplanted kidneys, in Starzl, T. E.: Experience in renal transplantation, Philadelphia, 1964, W. B. Saunders Co.
13. Porter, K. A., Calne, R. Y., and Zukoski, C. F.: Vascular and other changes in 200 canine renal homotransplants treated with immunosuppressive drugs, Lab. Invest. 13:809, 1964.
14. Porter, K. A., Thomson, W. B., Owen, K., Kenyon, J. R., Mowbray, J. F., and Peart, W. S.: Obliterative vascular changes in four human kidney homotransplants, Brit. M. J. 2:639, 1963.
15. Schilling, J. A., Shurley, H. M., Joel, W., White, B. N., and Bradford, R. H.: Abdominal aortic grafts: Use of in vivo structured autologous and homologous fibrocollagenous tubes, Ann. Surg. 159:819, 1964.
16. Schwartz, S. I., Kutner, F. R., Neistadt, A., Barner, H. B., Resnicoff, S., and Vaughan, J.: Antigenicity of homografted veins, Surgery. In press.
17. Szilagyi, D. E., McDonald, R. T., Smith, R. F., and Whitcomb, J. G.: Biologic fate of human arterial homografts, Arch. Surg. 75:506, 1957.
18. Todd, I. A. D., and Boctor, Z. N.: Experimental homotransplantation of arteries, Transplantation 4:123, 1966.
19. Vickery, C. M., McCombs, H. L., and Warren, R.: Experimental small-artery grafts in dogs treated with immunosuppressive drugs, New England J. Med. 272:1345, 1965.
20. Wright, I.: The microscopical appearance of human peripheral arteries during growth and aging, J. Clin. Path. 16:499, 1963.

Book review

A PRIMER OF ELECTROCARDIOGRAPHY. By George E. Burch, M.D., and T. ... Winsor, M.D. ed. 5. Philadelphia, 1966, Lea & Febiger. 301 pages, 28? illustrations. Price $6.50.

Th. fifth follows the fourth edition after ... interval of 6 years. All previous ed.tions were ... ell received on an i ternational sc le ... th t ... lat ons into the French, Spanish, It ... Czechoslovakia, Serbo-Croatia ... nd J panese languages. The ... hanges from the fourth ed t ... light ... as ... ta ed ... the pref ce ther ... has been no essential ... hanges ... the basic concept or fundament ... of ... lectrocard ogr ph ... before the book is one of the best ... troduct ry text ... ailable. It describes the basic principles (electroph siolog ... basis nomencl ture ... measurements) nd the ma ... t pes of lectr ardiogr phic ... bnormalities ... le ... nd ... ily understandable manner. The ... lectrocardiogr ph ... teria listed in the ... ppend ... pages 291-295 are useful for ... ystematization of interpretation. The detailed breakdown ... of lectrocardiographic normal standards by ... ge up to the ... ge of 20 years ... is ... ilable; however, larger normal samples (and therefore, more reliable ... lues) ... re available for the age group 20-30 ... ears. Unfortunately, ... no ... lues from ... ge groups over 30 ... ears are included, ... lthough highly signific ... t ... hanges oc ur after the age of 30 years. Differences due t ... sex are ... lso not considered, but their ... nclusion may go beyond the limitations of ... primer. Of ... nterest is the opinion of the ... thors that ... the f ndamentals of ... ectorcardiography ha ... not ad anced sufficiently t ... require changes in this field, ... nd that ... t the present ... tat ... ectorcardiography cannot serve physicians sufficiently to justify its ... linical use. The presentation of vectorcardiograph ... therefore is limited t ... 10 pages. It is ... nderstandable that the Wilson-Burch lead ... ystem is ... sed as ... eference, ... although ... t is rarely applied today. The ... ent ... mt ... n the presentation of vectorcardiography is remarkable in ... iew of the contributions of Burch ... nd associates t ... the early dev lopment of ... linical ... ectorc rdiography. Surprisingly, the discussion of the frontal plane ... entricular gradient (pages 258-272) is given more ... pace than th t ... llotted t ... the discussion of vectorcardiography. Rece t large-scale in estigations, particularly by Pipberger ... nd associates, ha ... hown that the frontal plane ... entric lar gradient has little diagnostic ... alue. Its use has declined over the past 20 y ... ; ... v ... ectorcardiography is being used now on an infinitely larger scale than is the ... entricular gradient. Missing is a reference to the electrocardiogr ph ... exercise test. The widespread ... linic l use ... nd diagnostic usefulness of this test would ha ... merited ... brief discussion even in ... primer.

The reviewer wishes t ... point out that this criticism does not reflect ad ersely on the basic merits of the book ... nd there is little doubt that this new edition ... ill be as eagerly ... nd favorably recei ed by the new generation of ... lectrocardiog ... phers as ... as the previous ones.

Announcements

THE SECOND ANNUAL CONFERENCE ON CARDIOVASCULAR DISEASES will be held March 23-25, 1967 at the Nugget Con ention C ... ter, Sparks, Nevada. The Conference is being sponsored by the Nevada Heart Association, Washoe Medical Center, Reno, Nevada, the Laboratory of P thophysiology of the Desert Research Institute of the University of Nevada, and the Nevada Stat ... Health Department, Reno, Nevada.

A CONFERENCE ON THE MICROCIRCULATION AS RELATED TO SHOCK, sponsored by the N tional Academy of Sciences—N tional Research Council ... nd the Graduate School of Boston Uni ersity ... ill be held ... t the Charles River Campus, Boston University, Boston, Mass., March 29-April 1, 1967.

Additional information can be obtained by ... riting t ... Dr. Da id Shepro, Boston Uni ersity Biological Science Center, 2 Cummington St., Boston, M ... s. 02215.

The Division of Postgraduate Education of the University of Florida College of Medicine, Gainesville, Florida, has sched led a semina ... on CARDIAC EMBRYOLOGY AND PATHOLOGY OF CONGENITAL HEART DISEASE t ... be held on Mar h 2-4, 1967.

American Heart Journal

March 1967 Volume 73 Number 3

Editorial

Angiography: Advantages and hazards

Johnson McGuire, M.D.
*Te Chuan Chou, M.D.***
Cincinnati, Ohio

Remarkable advances have been made in roentgen techniques for visualizing the major arterial pathways of the human body by the use of radiopaque contrast media since the publication on coronary arteriography in man by McClure and associates[1] in 1950. With safer contrast material and selective arteriograms making possible more accurate diagnoses, steady progress has been made in the treatment of cerebrovascular insufficiency due to obstruction of extracranial arteries, expanding intracranial lesions, and cerebral aneurysms, in the cure of hypertension resulting from renal ischemia, in operative treatment of congenital and acquired heart disease, and in the surgical cure of thoracic and abdominal aneurysms. There has also been significant improvement in the treatment of certain forms of peripheral vascular disease due to arteriosclerotic occlusion of large arteries with arteriotomy or bypassing techniques using grafts. Also encouraging progress has been reported in the surgical correction of mesenteric vascular obstruction causing abdominal angina. The diagnosis and localization of pulmonary embolism has recently been made possible by selective angiography of the pulmonary arteries and occasionally embolectomy has been successful in such cases. The development of selective coronary arteriography has revived efforts to revascularize the ischemic heart muscle. When surgical treatment of aortic stenosis is contemplated, coronary arteriography may demonstrate extensive coronary artery disease and contraindicate operative treatment.

However, the risks inherent in angiography raise questions concerning indications for the procedure. In many instances, angiography has become routine when there is any evidence of arterial ischemia. Frequently little consideration is given to the complications involved in these investigations. The hazards include death due to sensitivity to the contrast media, the creation of dissecting aneurysms resulting from perforation of the intima of diseased vessels by the tip of the catheter, or the production of dangerous and possibly fatal arrhythmias, especially in coronary artery visualization.

Complications of angiography

CONTRAST MEDIUM. The newer contrast media such as diatrizoate (Hypaque), sodium iothalamate (Conray), and methyl

Received for publication July 29, 1966.

*Professor of Medicine and Director, Cardiac Laboratory, University of Cincinnati College of Medicine, Cincinnati, Ohio.

**Assistant Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

glucamine diatrizoate (Renografin) are far superior to the older preparations and allergic or toxic reactions involving renal and nervous tissue formerly not uncommon are now extremely rare.

LOCAL PROBLEMS IN INSTRUMENTATION. The Seldinger technique for angiography has largely replaced translumbar aortography but has occasionally been complicated by severe local hemorrhage, arterial thrombosis and the production of dissecting aneurysms by the tip of the catheter.

CARDIAC DISORDERS. Cranger has reported that in 473 patients right heart catheterization with angiography was thought to be responsible for 2 deaths. Catheterization of the left side of the heart in 196 patients resulted in 1 immediate death possibly due to electrocution caused by faulty grounding of the electrocardiograph.

Lang[3] has reported from a questionnaire to 300 radiologists in the United States the results of 11,402 instances of retrograde aortography and arteriography. Seven deaths which were related to the procedure occurred in this series with 81 serious and 325 minor complications. Arterial thrombosis at the site of puncture was the most common serious complication occurring in 47 cases. Others were breakage of the guide wire or catheter, arterial embolism, perforation of major vessels, necrosis of the bowel, and renal shutdown.

Value of coronary cinearteriography in the investigation and treatment of coronary artery disease. In many large medical centers in this country and abroad there has been an increasing interest in coronary artery visualization due in large part to the brilliant studies of Mason Sones, of the Cleveland Clinic. Determination of the location and extent of coronary obstruction is indispensable prior to surgical treatment of the disease. If the lesion is limited to the anterior descending branch of the left coronary artery with some collateral circulation below the obstruction, transplantation of the internal mammary artery into a tunnel made in the myocardium (a technique utilized first by Vineberg of Montreal) may provide an additional supply of blood to the ischemic myocardium. That a high proportion of such grafts produce collateral circulation has been shown by the injection of contrast medium into the internal mammary artery several months after implantation of the grafts into the myocardium. Although a number of patients have shown clinical improvement, this operation must still be regarded as being an experimental procedure. When a coronary arteriogram demonstrates obstruction to the three major branches of the coronary artery, operative treatment has been generally considered to be contraindicated. However, several procedures employing arterial or venous grafts[4] to revascularize the posterior wall of the left ventricle are currently being investigated. Certain localized obstructions may be relieved by opening the coronary artery at the site of the lesion and enlarging the narrowed lumen by placing a graft of pericardium at the site of the arteriotomy or actually removing a thrombus. A number of patients have shown definite improvement after these procedures, although the mortality has been high with the direct approach.

Coronary arteriography is not entirely without risks, some of which may be quite serious. Sones has examined 6,400 patients by selective coronary arteriography employing a special catheter which he designed for this purpose. To date 7 deaths which were related to the procedure have occurred in this series, 3 in the first 1,000 studies and 4 in the last 5,400. Early in these studies 70 per cent of the brachial arteries were thrombosed, but in the last 1,000 cases, brachial occlusion occurred in less than 2 per cent. Ventricular fibrillation occurred in 84 instances; in 80, defibrillation using direct current restored normal rhythm; fatal asystole developed in 2. On four occasions a dissecting aneurysm of a coronary artery was caused by the catheter as it entered the orifice of a coronary artery, but was fatal in only 1 case.

Higher mortality and morbidity have been reported in other studies on coronary arteriography and emphasize the fact that when the technique is skillfully employed, as in the hands of Sones, it will cause far fewer complications than when performed by less experienced investigators.

Considerable difference of opinion still

exists in regard to the role played by disease of the very small coronary arteries, in the absence of obstruction of the large branches in the causation of angina. Many of the tiny arterioles, important for collateral circulation in patients with ischemic heart disease, have been beautifully demonstrated by Baroldi[7] employing injection of a plastic material in postmortem studies of the human heart. Such small collateral channels undoubtedly of importance in myocardial perfusion cannot be visualized by coronary arteriograms. Proudfit and associates have reported the correlation of effort angina with the demonstration of significant coronary artery obstruction by coronary cineangiography in 95 per cent of the cases studied and obstructive disease was correlated with myocardial infarction in 99 per cent. Angiographic findings correlated less well with the clinical diagnosis of atypical angina or coronary artery insufficiency. Future observations should be helpful in determining the number of false-positive and false-negative diagnoses in atypical angina.

Since coronary artery disease with intractable angina cannot be treated very satisfactorily by medical means at the present time carefully planned surgical efforts to promote collateral circulation may be warranted in selected cases until satisfactory prophylaxis of coronary atherosclerosis becomes a reality. Such surgical treatment should be limited to medical centers in which the operative procedure and postoperative evaluation are conducted by capable cardiac surgeons and cardiologists who have had an extensive experience in the treatment of coronary artery disease. An evaluation of the improvement in angina resulting from any form of treatment has been shown to be extremely difficult as exemplified by the temporary enthusiasm several years ago for ligation of the internal mammary artery in the cure of angina.

The history physical examination and electrocardiograms of the patient usually provide adequate evidence whereby an experienced clinician can establish the diagnosis of coronary artery disease without resorting to angiography. The use of cineangiography merely to provide an academic demonstration of an obstructed coronary artery is unwarranted in our opinion unless it seems to be probable that such a demonstration may establish the location and extent of coronary obstruction and clarify indications or contraindications for surgical treatment. When the diagnosis of chest pain is obscure coronary arteriography may be helpful in implicating or ruling out coronary disease as the etiological factor.

Conclusion. Angiography is of great diagnostic value but is associated with unavoidable risks to the patient. It is important that the patients subjected to angiography be carefully selected. The essential criterion for such a procedure should be the possible benefit to the patient and not that of academic diagnostic interest.

REFERENCES

1. McGuire, J., Helmsworth, J. A., Felson, B., and Scott, R. C.: Visualization of the coronary arteries during life. T. A. Am. Physicians 63:247, 1950.
2. Grainger, R. G.: Complications of cardiovascular radiological investigations. Brit. J. Radiol. 38:201, 1965.
3. Lang, E. K.: A survey of the complications of percutaneous retrograde arteriography. Radiology 81:257, 1963.
4. Pearce, C. W., Hyman, A. L., Brewer, P., Smith, P. E., and Creech, O. J.: Myocardial revascularization. Implantation of intercostal artery. J. Thoracic & Cardiovas. Surg. 52:809, 1966.
5. Ferlic, R. M., Quattlebaum, F. W., and Lillehei, C. W.: Experimental and clinical results of myocardial revascularization with "arterialized" autogenous vein graft. J. Thoracic & Cardiovas. Surg. 52:813, 1966.
6. Sones, F. M.: Personal communication.
7. Baroldi, G.: Myocardial infarct and sudden coronary heart death in relation to coronary occlusion and collateral circulation. Am. H. J. 71:826, 1966.
8. Proudfit, W. L., Shirey, E. K., and Sones, F. M.: Selective cine coronary arteriography. Correlation with clinical findings in 1,000 patients. Circulation 33:901, 1966.

Clinical communications

Renal artery anomalies and hypertension

A study of 340 patients

Philip W. Robertson, M.D., F.R.C.P.
*David H. Hull, M.A., M.B., M.R.C.P.**
*A. Klidjian, M.B., F.R.C.S.***
M. L. Dyson, D.M.R.D.
Wolverhampton, England

For some years we have been interested in the renal arterial pattern in hypertension. In an earlier paper[1] we discussed the assessment and treatment of hypertension and drew attention to the frequent finding of arterial anomalies in our patients. Furthermore, we showed that in our study of 121 patients those in whom no conventional cause for hypertension could be demonstrated showed a higher incidence of multiple arteries than the remainder (70 per cent in the idiopathic group, 40 per cent in the secondary hypertension group) and far higher than the usual estimated incidence in routine necropsy of around 26 per cent (quoted by Boijsen[2]).

Our earlier observations were made on a relatively small series; in subsequent years we have continued to study the arterial pattern of all hypertensive patients investigated at this hospital and a further 340 patients have been fully investigated for hypertension by methods similar to those which we described earlier.

Although our earlier ideas were, to us, original, we later found that attention had been drawn to the association of multiple arteries and hypertension many years before by Marshall on the basis of a large series of necropsies. Recently, Davis and associates published a paper on angiographic studies of 352 patients, of whom 252 were hypertensive. These authors stated: "This study supplements previous anatomic and angiographic work in showing that the arterial supply to the kidneys is frequently variable and that multiple renal arteries are more often found in hypertensive than in normotensive patients."

The significance of our earlier observations, and indeed those of Davis and associates, was recently questioned by Davies and Sutton,[5] but for reasons already published we did not consider their arguments to be valid.

We now wish to present further evidence of the association of multiple renal arteries and hypertension.

Material

For the purposes of this communication the angiograms on 340 patients with hypertension have been studied. These patients were derived from a wide variety of sources,

Received for publication April 26, 1966.
*Wing Commander, Consultant Physician, Royal Air Force Hospital, Cosford, Wolverhampton, Staffs., England.
**Squadron Leader, Senior Specialist in Medicine, Royal Air Force Hospital, Cosford, Wolverhampton, Staffs., England.
***Group Captain, Consultant Surgeon, Royal Air Force Hospital, Cosford, Wolverhampton, Staff., England.
****Consultant Radiologist, Wolverhampton and Dudley Hospital Groups, Staffs., England.

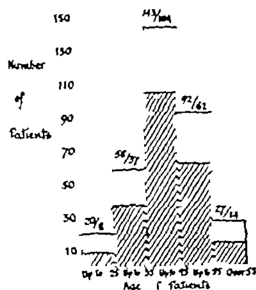


Fig. 1. Age distribution of 340 patients with hypertension. Proportion with idiopathic hypertension is shown by hatched area.

both service and civilian R.A.F. aircrew were referred from other service institutions whereas civilian aircrew came to us at the request of the Ministry of Aviation. Many service and civilian patients who were not flying personnel were referred from other service and civilian consultants and of course a proportion was seen through our own outpatient clinics and by reference from local practitioners and consultants.

Approximately 25 per cent of the patients in this series were females the patients ages ranged from 9 to 64 years at the time of our investigation with a mean of 45 years (Fig. 1).

It is important to recognize the difficult in describing accurately the age distribution of a series of patients with hypertension. In some instances the hypertension may have arisen only at about the time of the investigation in others it may have been known to be present for years, and in some the date of onset of hypertension cannot be determined. In civilian practice it is frequently impossible to date the onset accurately because of the relative rarity of routine medical examinations, although among civilian aircrew this is not so. Most service personnel have some record of a blood pressure reading in their medical documents. In the case of women of child-bearing age, routine antenatal examinations are of considerable help in obtaining past records and may date the onset of hypertension quite accurately.

We believe that it is unwise to attach too much significance to the age of the patient. In most instances hypertension produces no symptoms so that the age at the time of discovery merely represents the age at which a chance discovery is made or some complication occurs. There is frequently evidence to suggest that the blood pressure has been above average for very many years before full investigation takes place. In this series, the figures refer only to the age at the time of our investigation.

Recent work has underlined the sharp variation in levels of blood pressure in patients in whom a 24-hour recording was possible. A wide range of blood pressures recorded from the same patient under different conditions of activity and the influences of rest, sedation, and sleep, all combine to make an exact definition almost worthless. In a number in our own series the levels were not very high and in some of these obesity emotional factors, alcohol and other features classically associated with labile pressure were noted. These patients tend to produce negative results from their laboratory and radiologic investigations, and so diminish the percentage of positive findings. There is no easy way to exclude such patients from the series, and no attempt has been made to do so this paper describes a consecutive series of patients examined over a period of about 3 years, with blood pressure levels above 150/100 mm. Hg under normal circumstances. The great majority of the patients had much higher levels, with diastolic pressures usually about 120 mm. Hg the criteria are as given in our 196_ paper.

Our paper largely concerns the association of renal artery anomalies with idiopathic hypertension. The full findings from our investigations are therefore not relevant, but it may be noted that in 25 patients, or 66 per cent, no conventional explanation for hypertension was forthcoming and this group would usually be referred to as having "essential" or

idiopathic hypertension. The remainder was regarded as having secondary hypertension. Their age distribution is included in Fig. 1. It is amongst the idiopathic group that anomalies of the renal arteries seem to be particularly prevalent.

Before we undertook this work we might well have had much less difficulty than we do now in classifying hypertension as idiopathic ("essential") or as secondary. Clearly the whole question hinges on whether certain findings are accepted as a probable cause for hypertension. In this paper we have continued to assume that an anomalous arterial supply is not as yet accepted as an etiological factor (although it will be seen that we do consider the association to be significant).

Furthermore, since all grades of renal maldevelopment are found, it may be difficult to decide at what point it would be conventional to link such anomalies with coexisting hypertension. For example, in most circumstances a double pelvis and ureters would not be thought to be significant, whereas a horseshoe kidney would be. A very small kidney is usually accepted as a factor in hypertension, but there can only be an arbitrary decision on how small the kidney must be for acceptance as a conventional factor. In many instances, we have reinvestigated patients who in past years had been shown to have a small kidney and hypertension, but those responsible at the time had not accepted an etiological link. In subsequent investigation we have thought renal hypertension to be present—but to classify now such a patient as having a conventional explanation for the hypertension may seem to be unreasonable. In general, we have tried to adopt a view as orthodox as possible in listing the types of hypertension, assuming at this point that minor renal anomalies and arterial variants are not relevant.

Methods

All of our patients were extensively investigated—not only from the renal but from the general medical viewpoint. An aortogram was obtained in every case and invariably by the femoral retrograde route, for we believe that only by this route can one hope to demonstrate adequately widely spaced multiple renal arteries or other intra-abdominal anomalies. We do not favor the translumbar route for routine use. Selective angiography was used most sparingly and then only to elucidate further some point demonstrated by full routine angiography. Similar views are quoted elsewhere—for example, by Kincaid.

Femoral route angiography appears to be a remarkably safe procedure; we have now recorded well over 1,000 angiograms with little significant morbidity. This experience seems to be at variance with that quoted by Chamberlain and Gleeson,[8] who claimed a complication rate of 12.4 per cent. There are many possible explanations for this—differences in interpretation of complications, differences in technique, in types of catheter used, and so on. This communication is not the place for detailed discussion on the technique of angiography—but we are convinced that the femoral route using the Seldinger technique is safe, simple, and satisfactory. On very few occasions has it proved to be impossible to pass the catheter up the aorta, and the route has been used for many other procedures besides renal angiography. Thus peripheral limb angiography, coronary angiography, sometimes carotid, vertebral, or left ventricular angiography can be completed by the same route. The Schönander serial changer continues to work well and requires little attention, providing a thoroughly reliable and technically satisfactory service.

Results

Multiple renal arteries were demonstrated in a total of 164 patients, or just under half of all those investigated. In approximately one quarter of those with multiple arteries the anomaly was bilateral. In addition to those with multiple arteries, very early arborization was noted in a further 27 patients. Obviously early branching may be variously interpreted; we have reserved the term for those in whom branching occurs from the first centimeter of the main renal artery. There may be associated atypical segmental arterial branching.

The distribution of these findings in relation to etiological factors is shown in

Table I

	Total number of patients	Multiple arteries	Early branching	Total with arterial anomaly
Idiopathic hypertension	225 (66)	134 (60)	18	152 (67)
*Secondary hypertension	115 (33)	30 (26)	9	39 (34)
Total	340	164 (48)	27 (8)	191 (56)

*Figures in parentheses are per cent.

Table I In this table all percentages are approximate Where multiple arteries are present on one side and early branching on the same or other side only multiple arteries are listed Similarly of course the list concerns number of patients, and bilateral multiple arteries are not listed twice.

Distribution of arterial anomalies according to age showed no special characteristics and followed the age distribution of the whole series (Fig 2)

We make no attempt to provide a control series of angiograms of normotensive patients with which to compare our findings The world literature contains many and varied estimates of the over-all incidence of multiple arteries although it must be remembered that in very few has the estimate been related to the presence or absence of hypertension. In none has the incidence been nearly so high as in our series—20 to 30 per cent is the usual estimate

It should also be noted that in some papers dealing with angiographic findings (e.g Davis and associates[4] and Davies and Sutton) the facts are presented from a purely radiologic aspect. In our view the incidence and significance of multiple renal arteries in hypertension becomes striking only when careful analysis of every aspect of each patient has determined a likely etiological basis, leaving an idiopathic group containing the highest proportion of arterial anomalies.

Types of anomaly

Most commonly seen were accessory lower pole arteries arising from the aorta below the normal renal level (Fig 3) Sometimes this was as far down as the

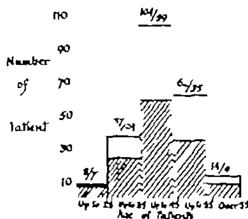


Fig 2 Age distribution of idiopathic hypertension (taken from Fig 1), showing proportion with multiple arteries (*hatched area*).

bifurcation of the aorta or even from one of the iliac arteries. It sometimes was possible to forecast a multiple arterial supply from the shape of the renal outline in many cases the outline was less reniform and more sausage shaped (Fig 4) Occasionally we have noted a renal shape suggestive of multiple arterial supply and yet only a single artery is present sometimes in these patients the renal artery may arise from one point but soon divide to resemble the multiple arterial pattern Sometimes quite bizarre renal shapes were noted with multiple renal arteries, being associated with more florid congenital variations (Figs. 5A and 5B)

Only on rare occasions have accessory arteries been found to arise from above the normal level an important point when one is considering the position at which the catheter should lie. We normally try to avoid filling the mesenteric and other



Fig 3 Accessory artery to lower pole of right kidney in 23-year-old man. Symptomless persistent hypertension of idiopathic type.



Fig 4 Bilateral multiple arteries in 41 year-old woman with idiopathic hypertension. The rather "sausage-shaped" renal outlines are often seen with multiple artery pattern.

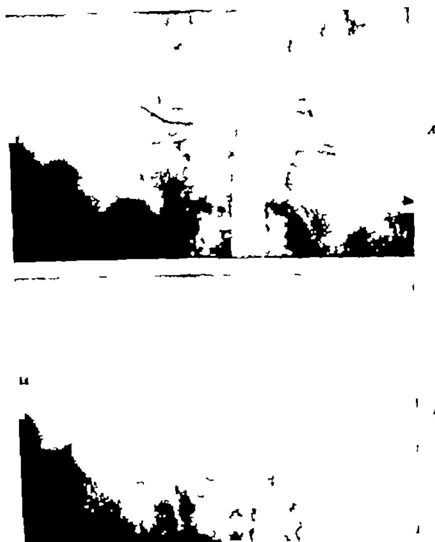


Fig. 5A Bilateral multiple arteries—arterial phase.

Fig. 5B Bilateral multiple arteries—nephrogram phase. Thirty-five-year-old man with symptomless proteinuria and hypertension.

visceral arteries arising from above the normal renal level and it seems to be unlikely that many accessory arteries would be missed by this method.

Arterial patterns were sometimes abnormal on both sides—two or three arteries on each side may be demonstrated (Figs. 4 and 8). In some of these cases it may not be easy to see clearly the point of origin since the vessels may not arise from the true lateral wall of the aorta; it may therefore be difficult to decide whether there is any significant ostial stenosis on radiologic grounds alone.

Associations of multiple arteries with other disorders

Arterial anomalies were sometimes found in patients with recurring infection of the renal tract. In these circumstances, the renal infection which obviously could not have preceded the developmental abnormality might have been regarded as the only factor in the etiology of the hypertension had not angiography revealed the multiple arteries.

The association of multiple arteries, hypertension, and renal infection in pregnancy (Fig. 6) has been of particular



Fig. 6. T renal arteries on right side rather small scarred right kidney and normal left side in 28-year-old woman. Pyelitis of pregnancy at 20 years with first pregnancy. Similar trouble with second pregnancy and recurring urinary symptoms and hypertension had followed her third and last pregnancy at 25 years of age.



Fig. 7. Multiple renal arteries on the right side there was double pelvis and ureter on this side. Forty-five-year old man with severe hypertension presenting with cerebrovascular accident.



Fig. 8 Bilateral multiple arteries in a 33-year-old man with persistent hypertension. This patient presented with subarachnoid hemorrhage from a congenital aneurysm which was treated surgically. The association may be coincidental.

interest. Many examples of this association have been seen and will be the subject of a later publication. The association of multiple arteries with other abnormalities of the genitourinary tract has been common. Thus, in horseshoe kidney, pelvic kidney, and double ureters with or without duplex kidney, arterial abnormalities may be found (Fig. 7). Other congenital arterial anomalies may be present (Fig. 8).

Accessory arteries have rarely been found to produce any significant disturbance in renal pelvic drainage and the association of arterial and pelvic anomalies was most unpredictable.

Discussion

The presence of multiple arteries represents incomplete development. The normal embryological processes involve the ascent of primitive renal tissues, together with their blood supply, derived in the early stages from arteries in the immediate neighborhood—the middle sacral and common iliac arteries. The definite renal artery is not recognizable until the beginning of the third month of intrauterine life, and then is usually formed from the most caudal of the three suprarenal arteries. Additional renal arteries persisting into the fully formed fetus represent persisting *mesonephric arteries.*[10]

Many congenital malformations of the renal tract are recognized and with some of these hypertension is an accepted association. Thus, in horseshoe kidney, plate kidney, pelvic kidney, and "hypoplastic" kidney hypertension is common; arterial anomalies are also common in such patients. Lesser abnormalities are often found—double ureters, "duplex kidneys," malrotated and misshapen kidneys—and sometimes here too arterial anomalies are associated. One may speculate that intrarenal and functional changes can occur in the absence of gross renal abnormality, and it is our belief that the likely significance of multiple renal arteries lies in *microscopic or submicroscopic renal* changes rather than in any direct circulatory effect of the large-artery pattern. There seems to us to be a distinct possibility of microscopic circulatory disturbances; however, abnormalities in the juxtaglomerular vessels could perhaps be related to abnormality of blood pressure regulation. Unfortunately, we have no direct evidence that this can be the case.

This view of renal dysplasia associated with arterial anomaly has been encouraged



Fig 9A Magnification ×250 A h line glomerulus is surrounded by numerous lymphocytes. (This cellular rea tion is regarded as being NOT inflammatory) There are sinusoidal vessels near the capsules. In some areas there is general absence of parenchymal tructures.

by other factors—in some of our patients, nephrectomy specimens have shown histologic appearances similar to those de scribed by Marshall [1,2] Thus, there may be scattered small hyaline glomeruli abnormal tubules and lymphocytic infiltra tion (Figs. 9A and 9B) Such changes might be regarded by some as representing chronic infection or the effects of hypertension but it is at least arguable that such a histologic pattern represents renal dysplasia In the particular case illustrated a 42 year-old man was shown to have multiple arteries supplying a normal-sized right kidney There was no irregularity of the nephrogram outline on either side—*on the left there was a normal* arterial pattern No clinical radiologic or labora tory evidence of renal infection or other abnormality was present

The relationship of renal dysplasia to infection may be significant. In a number of our patients, chronic *or recurrent* infec tion was present in a kidney with multiple arteries. Fig 6 illustrates this point—a woman in whom pyelitis of pregnancy led to recurrent infection and later evidence of chronic infection in the small (right) kidney with arterial anomalies and the associated estal lished hypertension

It has not been possible with existing methods to determine whether a kidney with multiple arteries is a direct cause of hypertension Di ided renal studies are not sufficiently sensitive in our experience (which is considerable—over 150 patients have had divided studies) to provide reliable information on minor functional changes So often a kidney may be much smaller than its fellow and not surprisingly give different clearances but this cannot be taken as a reliable gu de to the cause of hypertension

Nor can radioactive studies give direct evidence. We believe that misleading deductions may be made from analysis of



Fig 9B Magnification ×250 There are sinusoidal vessels near the capsule. An abnormal tubule sweeps around cystic glomerular capsule containing tiny trophic tuft—this is reminiscent of the fetal structure. There is scattered lymphocytic infiltration

such studies when there is a marked difference in the size of the kidneys, when there are gross arterial developmental abnormalities, or when there is more than one disorder present on one or both sides. What is needed is some method of direct assessment of altered renal function—for example by measurement of hypertension-producing substances formed in one or the other kidney We have for some years planned to undertake differential renal vein angiotensin studies but this has not yet proved to be practical a recent paper from Crollman's unit[18] has provided striking results from such procedures. Until such methods are generally available firm proof of the renal origin in some of these patients will not be obtained other than by the therapeutic test of nephrectomy when this seems to be justifiable

Nonetheless, it remains difficult to disregard the findings of multiple renal arteries in a young healthy adult in whom exhaustive tests can provide no evidence of any possible cause for established hypertension. When this pattern is repeated time and again the case fo an etiological link becomes strong

The demonstration of a pattern of multiple arteries can have special surgical significance. If renal grafting is contemplated it is obviously desirable to know in advance the arterial pattern of the donor and recipient. Again in patients in whom nephrectomy is considered it is helpful to know the arterial pattern of the contralateral side since a grossly abnormal arterial pattern there would necessitat caution even though the kidney be functionally normal.

Stenosis of an accessory renal artery has frequently been illustrated in t medical literature (examples m in textbooks journals

renovascular hypertension and illustrations in surgical works on vascular techniques) and this stenosis has been described as the cause of the hypertension yet no stress has been laid on the association with multiple arteries, which could be of etiological significance

Schwartz and White recently commented upon the apparent lack of close association between renal artery stenosis and hypertension in a large series of necropsies and in subsequent correspondence[14] we supported this view believing that renal artery stenosis alone is a rare cause of hypertension

The significance of these angiographic findings could be very great For years discussion on the possible nature of essential hypertension has continued There are those who appear to believe that the condition does not exist at all whereas others have attempted to identify some pattern of inheritance or special distribution in the population Yet these observations are made on inadequately investigated patients—unless each has been subjected to angiography the association with arterial anomaly cannot be determined We believe in fact, that not only would arterial anomaly be revealed in many of these patients, but numerous other findings, such as fibromuscular dysplasia renal artery obstruction and congenital renal abnormalities would emerge Attempts have been made to define indications for angiography in hypertension—but in our view without angiography investigation is incomplete and no discussion on the nature of essential hypertension can be realistic and no conclusion valid

Suggestions by Chamberlain and Cleeson[9] that little therapeutic benefit may result from angiography in hypertension are not in accordance with our experience. Their method of arriving at this conclusion is not, in our opinion, valid a retrospective analysis of the therapeutic benefits of surgery in those patients who were selected for angiography may be an unreliable guide It would be more to the point to consider what good might have resulted from full investigation of those who were not selected for many of our patients had been partially investigated elsewhere with negative results, but yet were shown on angiography to have an important and sometimes remediable disorder One of our most dramatic surgical successes of the whole series was just such a patient who had a cirsoid angioma and who had been investigated but not subjected to angiography at the unit from which Chamberlain and Cleeson write.

It seems to us to be quite possible that in some instances at least a family history of hypertension may be associated with an inherited pattern of renal development and we now have several clear examples of this association in which arterial abnormalities are present in more than one member of the family This may go some way toward supporting the view of Platt[17] that the idiopathic group of hypertensive individuals is distinct and does not consist of a heterogeneous collection of persons in whom there are as yet undetected disorders producing hypertension

Summary

Following an earlier paper we have studied a further 340 patients with hypertension. Renal angiograms were obtained in each instance Two hundred twenty five patients were assessed as having idiopathic or essential hypertension and of these 152 (67 per cent) were shown to have a renal arterial anomaly These figures correspond quite closely with those of the earlier smaller series in which the incidence was 70 per cent.

If the two series are taken together it is seen that in a total of 461 hypertensive patients, about 68 per cent of those with essential hypertension had renal artery anomalies.

The view that such arterial anomalies may be associated with renal dysplasia is presented and discussed

The findings support our view that the association between renal artery anomaly and idiopathic hypertension may be significant and confirm observations made by others in this field

Our continued thanks are due t the many members of the staff of this hospital who ha helped us, since our work would hav been impossible without the fullest cooperation of the laboratory the -ray department, nd the nursing staff Dr D D Hilton who was associated with the earlier paper continued to assist us ill completing his term of service in

the R.A.F. W are most grateful t M Wilfred Lee F I I P (Head of the Photographic Department of Liverpool University), for all of the illustrations and t the many practitioners and consultants who have referred these patients t us the Senior Civilian and Service Consultant to the R A F ha given us every encouragement. W thank the Director General, Medical Services, Royal Air Force for permission t publish

REFERENCES

1 Robertson, P W Klidjian, A., H ll, D H., Hilton, D D and Dyson, M. L. The assessment and treatment of hypertension Lancet 2:567 1962.
2 Boijsen, E Angiogr phic studies of the nat omy of single and m ltiple renal arteries, Acta Radiol Suppl. 183 1959
3 Marshall, A. G Aberrant renal arteries and hypertension Lancet 2 701 1951
4. Davis, G D Kincaid, O W and Hunt, J C. Roentgenologic evaluation of multiple renal arteries, Am. J Roentgenol. 90:583 1963.
5 Davies, E. R and Sutton, D Hypertension and multiple renal arteries, Lancet 1:341 1965
6 Robertson, P W Klidjian, A., Hull, D H and Dyson, M L Hypertension and multiple renal arteries, Lancet 1:536 1965
7 Round-the-clock blood-pressure, Brit. M J 2:526 1964
8. Kincaid, O W f Vuamonte, M J and Parks, R. E. editors Progress in angiography Springfield, Ill. 1964, Charles C Thomas, p. 280.
9 Chamberlain, M J and Gleeson J A. Aortography in the investigation of hypertension, Lancet 1:619 1965.
10. Gray Anatomy ed. 29 London 1946, Longmans, Green & Co.
11 Marshall, A. G. The persistence of foetal structures in pyelonephritic kidney Brit. J Surg 41:38 1953.
12. Marshall, A. G. Scar of the renal cortex, J Path. Bact. 71:95 1956.
13 M Pha l, J J J M Intosh, D A Williams, L. F Gritt, E. J Malette W G. and Grollman A. Pressor activity of renal venous blood in hypertension, Ann. Int. Med 61:847 1964.
14. Schwartz, C. J and White, T A. Stenosis of renal artery An unselected necropsy study Brit. M. J 2 1415 1964.
15 Robertson, P W Klidjian, A Hull, D H. and Dyson, M L. Renal-artery stenosis, Brit. M J 1 186, 1965.
16. Robertson, P W Hull, D H. Hilton D D Klidjian, A and Dyson M L. Developmental renal-artery stenosis, Lancet 2:661 1962.
17 Platt, R The natural history and epidemiology of essential hypertension, Practitioner 193:5 1964.

Pulmonary valve regurgitation secondary to bacterial endocarditis in heroin addicts

R. A. Massumi, M.D.
H. Just, M.D.
A. Tavakkol, M.D.
Washington, D.C.

Involvement of the endocardium of the right side of the heart in the course of bacterial endocarditis is encountered in only about 5 per cent of the cases. This is chiefly a reflection of the smaller incidence of congenital heart disease predisposing to right-sided endocarditis as compared with rheumatic heart disease, which is the main predisposing factor for left-sided endocarditis. Other important factors are the lower pressures to which the valves on the right side are subjected and the lower oxygen tension of the blood in the right side of the heart which discourages the aerobic bacteria. The overwhelming preponderance of the left side becomes less apparent when one considers only acute endocarditides caused by virulent microorganisms and therefore eliminates the importance of pre-existing endocardial lesions.[7] Staphylococcus, gonococcus, and pneumococcus represent such bacteria. The outstanding example of right-sided staphylococcal endocarditis is that which occurs in heroin addicts using unsterilized syringes and intravenous needles for self-administration. The great majority of such cases have been reported from our hospital[11] and the tricuspid valve has been the sole structure involved.

The 2 cases presented here with documentation during life are of special interest because they represent the only two examples of involvement of the pulmonary valve in right-sided endocarditis of heroin addicts, and the third and fourth cases of involvement of the pulmonary valve in staphylococcal endocarditis ever reported in the literature.

Case reports

Case 1. S. S., 32-year-old Negro woman, was first seen at the District of Columbia General Hospital in April, 1960, because of fever, cough, bloody sputum, and pain of 1 week's duration in the right side of the chest. The past history was one of heroin addiction for 10 years. She administered the drug by intravenous route, using unsterilized needles and syringes. The heroin powder was dissolved in a tablespoon in a small quantity of tap water, heated, drawn into the syringe, and injected intravenously. The use of the drug often occasioned small gatherings in which several addicts used the same tools for injection. She denied having had previous chills, fever, or any skin infection at the site of the needle punctures. Numerous needle puncture marks were found along the course of several of the superficial veins on both forearms. Cardiac examination at this time was unremarkable. A roentgenogram of the

From the George Washington University Division of Medicine and the Cardiopulmonary Laboratory, District of Columbia General Hospital, Washington, D.C.

Received for publication May 2, 1964.

*Chief, Cardiopulmonary Laboratory, District of Columbia General Hospital, and Associate Professor of Medicine, George Washington University School of Medicine, Washington, D.C.

**Cardiology Fellow, George Washington University Division of Medicine, District of Columbia General Hospital.

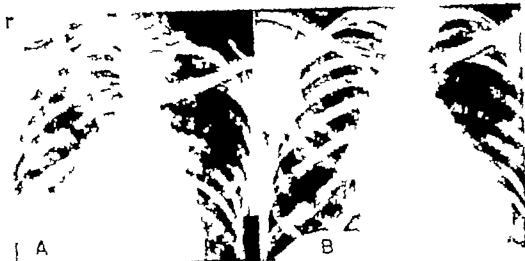


Fig. 1. Case 1. Chest roentgenograms taken during the acute phase of endocarditis (A) and 2 years later (B). Note the multiple densities in both lungs due to septic infarcts during the active phase of infection, and the increase in heart size in the later film.

chest showed pleural effusion on the right, and multiple nodular lesions in the lower lobes, consistent with septic infarcts originating from the endocardium of the right side of the heart (Fig. 1,A). Several blood cultures were positive for *Staphylococcus* coagulase positive for which she was treated with massive doses of penicillin.

On the fifteenth hospital day a soft pansystolic murmur was heard at the xiphoid area and was attributed to tricuspid regurgitation secondary to the acute right-sided staphylococcal endocarditis. During the ensuing 6 months she was seen twice in congestive heart failure, and a soft, Grade 2/6, pansystolic murmur of tricuspid regurgitation and diastolic gallop were heard. She responded to digitalis and remained free of symptoms until August, 1962, when she was rehospitalized for treatment of persistent heroin addiction. She reported that she had stopped taking digitalis and had remained asymptomatic.

On physical examination, her blood pressure was 110/70 mm. Hg, and the pulse rate was 90 per minute. She was thin, undernourished, young woman with moderate kyphoscoliosis. The lungs were clear by auscultation and on the roentgenogram (Fig. 1,B). Cardiovascular examination revealed prominent jugular *v* waves and forceful right ventricular heave. A Grade 4/6 pansystolic tricuspid regurgitation murmur was heard best at the xiphoid area, with radiation up along the left sternal border. The murmur did not change significantly during inspiration. Additionally, a short superficial, scratchy diastolic murmur of unusual quality and cadence was heard best in the third left intercostal space parasternally and only faintly in the surrounding area. This murmur began shortly after the second component of the second sound and ended before the following first sound. The pitch was neither the very low-frequency rumble of mitral stenosis and the high-frequency diastolic murmur of aortic regurgitation. The intensity increased markedly during inspiration (Fig. 2). An ejection type of systolic murmur was also audible in the third intercostal space. There were no peripheral manifestations of aortic regurgitation. An enlarged, pulsating liver was palpable 2 fingerbreadths below the costal margin. The electrocardiogram (Fig. 2) showed right axis deviation and significant right atrial enlargement, in comparison with the tracing taken during the 1960 admission.

HEMODYNAMIC STUDIES. Right heart catheterization revealed a high right atrial mean pressure, obliterated *x* descent, and very prominent *v* waves (Fig. 3). The right ventricular pressure was normal, but the pulmonary arterial pressure exhibited a low diastolic level. The configuration of pressure pulses from the right atrium, right ventricle, and pulmonary artery were almost identical, indicating extreme regurgitation at both the tricuspid and the pulmonary valves (Fig. 3).

Intracavitary phonocardiography (Fig. 3) clearly demonstrated a pansystolic murmur, a filling third sound, and an atrial gallop at the tricuspid valve area and an ejection type of systolic and a diastolic murmur in the cavity of the right ventricle just below the pulmonary valve. Beyond the pulmonary valve only the ejection systolic murmur could be recorded. The diastolic murmur recorded in the outflow tract of the right ventricle was crescendo-decrescendo of low frequency with some high-frequency components. It began at an interval of approximately 0.04 second after the sound of pulmonary valve closure, peaked approximately 0.08 second after onset, and lost its intensity at about the same rate. Selective dye curves with injection downstream of each valve and sampling upstream according to the method suggested by Bajec and associates and Collins and associates demonstrated regurgitation through both valves (Fig. 4).

The conclusion was that the patient had combined

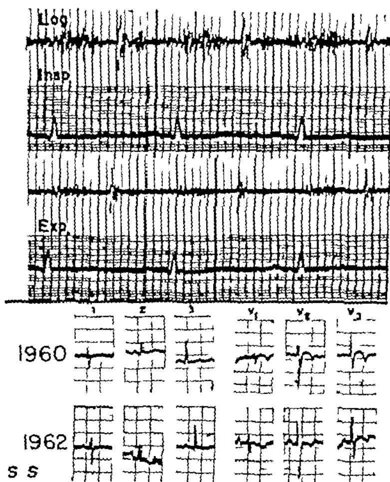


Fig. 2. Case 1. Top, Inspiratory and expiratory phonocardiograms recorded from the third left intercostal space depicting the ejection systolic murmur and the late low-frequency coarse diastolic murmur both of which are considerably louder during respiration. *Bottom*, Selected electrocardiographic leads taken 2 years apart show the occurrence of large P waves and tall R waves in Lead V indicating combined right atrial and ventricular hypertrophy.

tricuspid and pulmonary valve regurgitation of severe degree secondary to healed right-sided staphylococcal endocarditis.

Case 2. L. W., a 43-year-old Negro man, entered the District of Columbia General Hospital in August 1965 because of abdominal swelling which proved to be due to ascites related to biopsy-proved Laennec cirrhosis. Cardiac consultation was requested because of a diastolic murmur in the third left intercostal space. The blood pressure was 130/70 mm. Hg and peripheral pulses were of normal quality. The jugular venous pulse contour was normal, and the liver did not pulsate. The heart was normal in size, and the apical impulse was left ventricular. The right ventricular impulse was only moderately increased. The impulse of a dilated pulmonary artery could be felt and recorded in the second left intercostal space near the sternal edge (Fig. 5). Thrills were absent. The first and second heart sounds were of normal quality and the splitting of the second sound was physiological. A Grade 3/6, rough superficial, diastolic murmur was heard loudest in the third left intercostal space parasternally and only faintly in the second and fourth intercostal spaces. The murmur began 0.04 second after the pulmonary component of the second sound and was of crescendo-decrescendo configuration. It was greatly accentuated during inspiration, and at this time a Grade 2/6 ejection systolic murmur was also audible in the same area (Fig. 5). These characteristics of the murmur and the absence of peripheral signs of aortic runoff favored a diagnosis of pulmonary valve regurgitation and prompted a search for evidence of a healed right-sided endocarditis. The observation of linear needle marks along the veins of the dorsum of the left hand and left forearm led to the patient's prompt admission of heroin addiction. From 1940 to 1955 he had used heroin by a technique identical with that in Case 1. He had been treated in this hospital for

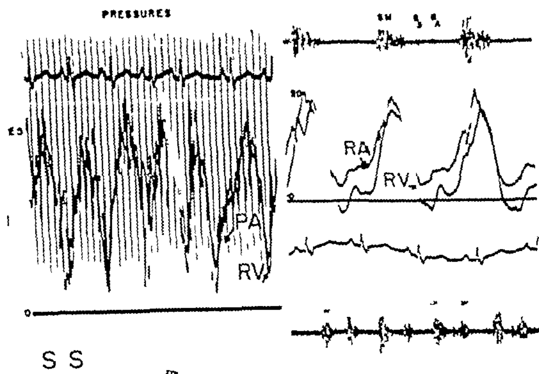


Fig. 3 Case 1. *Left.* Simultaneously recorded pulmonary arterial (*PA*) and right ventricular (*RV*) pressures show virtually identical configurations and suggest wide-open pulmonary valve regurgitation. *Upper right.* Tracing depicts intracardiac pressures from the right ventricle and right atrium recorded simultaneously with intracavitary phonocardiogram from the inflow tract of the right ventricle. Note the ventricularized configuration of the right atrial pressure pulse due to gross tricuspid regurgitation. *Lower right.* Intracavitary phonocardiogram recorded from the outflow tract of the right ventricle, clearly showing the diastolic murmur (*DM*) of the pulmonary valve regurgitation and also the ejection systolic murmur.

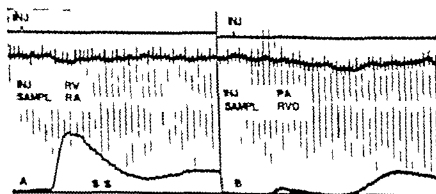


Fig. 4. Case 1. Selective dye curves across the tricuspid (*A*) and across the pulmonary valves (*B*). Note early regurgitation curves with injection of Cardio-Green just downstream from the respective valves. The late curves in both instances represent systemic circulation. Vertical lines are 1 second apart.

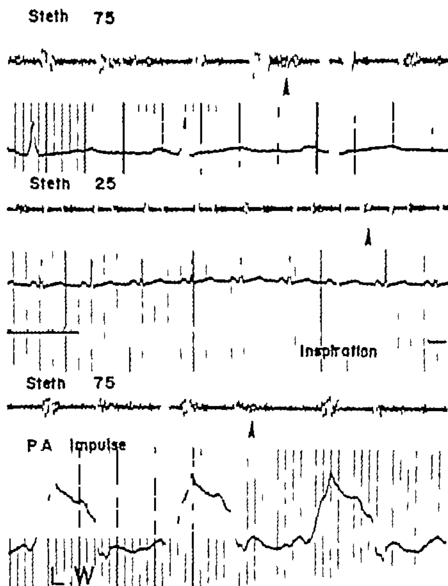


Fig 5 Case 2 Surface phonocardiogram *Top row* Taken during inspiration in the third left intercostal space shows the crescendo-decrescendo diastolic murmur with the same acoustical characteristic as the murmur in Case 1 A low-intensity systolic ejection murmur is also recorded. *Middle row* Same as top row taken at the slower speed of 25 mm per second allowing observation of inspiratory augmentation of the diastolic murmur (*arrow*). *Bottom row* Simultaneous recording of phonocardiogram with surface impulse from the second left intercostal space to the left of the sternum Note that impulses of arterial contour with a clear-cut dicrotic notch are recorded over the dilated main pulmonary artery

month in 194 for a condition described by him as "high fever chills, shortness of breath cough and blood spitting Unfortunately records and x-ray films are no longer available. However the patient did remember distinctly that he was treated with penicillin, and that his illness was preceded by an abscess that required drainage at the site of heroin injection on the left forearm. The pitted scar of this skin infection was still visible. In 1919 he was told for the first time in his life, that he had a heart murmur

A retrospective diagnosis of staphylococcal right sided endocarditis was thought to be eminently justified in view of the antecedent history of heroin addiction the abscess on the forearm the prolonged febrile illness marked by chest symptoms and hemoptysis good response to penicillin therapy and the subsequent discovery of a heart murmur

HEMODYNAMIC STUDIES. The right atrial, right ventricular pulmonary arterial, and wedge pressure pulses were of normal contour and magnitude. The normal pulmonary arterial diastolic pressure seg

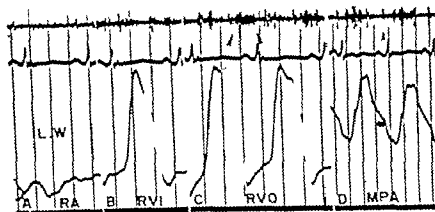


Fig. 4 Case 2. I tracardiary phonocardiograms recorded from the right atrium (*RA*) in A, from the right entricular inflow tract (*RVI*) B from the right entricular outflow tract (*RVO*) in C and from the mai pulmonary artery (*MPA*) D Note that the diastolic murmur (*large arrows*) is ery loud in the RV outflow tract but loses intensity rapidly as the catheter is moved way in either direction. The ejection systolic murmur is loudest in the main pulmonary artery and is undoubtedly secondary to the increased systolic flow across the pulmonary al as result of regurgitation. The small arrow in *D* points to ery loud trial gallop which is also depicted in the right atrial tracing

gested hemodynamically insignificant regurgitation (Fig. 6). I tracardiac phonocardiography demonstrated an ejection systolic murmur in the pulmonary artery abov the alve, and equally loud crescendo-decrescendo diastolic murmur that as maximal just below the alv in the outflow tract of the right entricle The latter lost intensity rapidly the tip of the catheter was withdra n toward the pex Passage of the catheter across the tricuspid val failed to record a significant murmur of tricuspid egurgitation.

Pulmonary angiography as then performed. The tip of the catheter as placed immediately bel the pulmonary valve nd after contrast medium had been injected into the main pulmonary artery egurgitation into the right entricle as observed (Fig 7). These findings substantiated the presenc of an isolated pulmonary alv regurgitation of moderate magnitude.

Discussion

All of the previously reported cases of staphylococcal endocarditis of heroin addicts that came to autopsy demonstrated lesions of the tricuspid valve alone and a diastolic murmur suggestive of pulmonary valve regurgitation has not been described in any of the survivors. As stated previously the organism responsible for endocarditis in heroin addicts has almost universally been staphylococcus (15 of 16 previously reported cases) and the cases reported herein follow the same rule Th s is n sharp contrast to the prevalence of streptococci and gram negative organisms



Fig 7 Case 2 Pulmonary angiogram with injection into the main pulmonary artery show g gross regurgitation of contrast medium into the right entricle.

n opium users even though both groups appear to employ identical techniques [13]

The feature of septic pulmonary infar ts so prominent n previous reports was present in the subjects of th s communication.

In fact the present cases are typical of the syndrome of right-sided staphylococcal endocarditis of heroin addicts in every respect save for involvement of the pulmonary valve which was the sole valve involved in Case 2. In this respect they resemble the cases of staphylococcal endocarditis in 2 non-addicts reported by Edwards[3] and by Levin and associates.[14]

The typical to-and-fro or systolic-diastolic murmur audible in the third left intercostal space at the sternal edge and unassociated with peripheral manifestations of an aortic runoff has again been demonstrated to be a reliable sign of pulmonary valve regurgitation. The hemodynamic studies in these 2 cases serve to support the oft-stated belief that the hemodynamic consequences of pulmonary valve regurgitation are well tolerated.[4,17] In fact the acquired lesion, as well as the congenital variety of pulmonary valve regurgitation, are often incidental findings in the course of cardiac examination. This is in sharp contrast to the hypertensive type of pulmonary valve regurgitation (Graham Steell murmur) in which symptoms of severe pulmonary hypertension

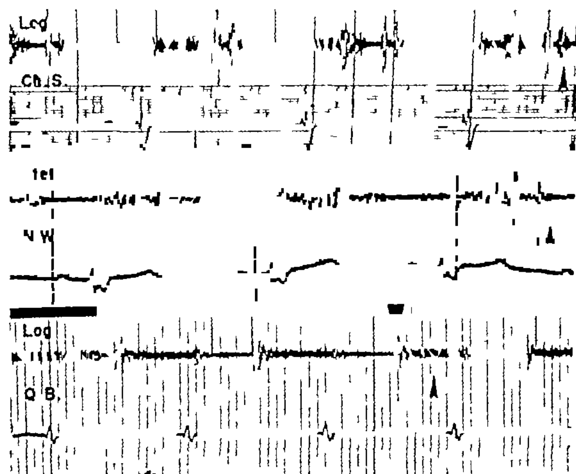


Fig. 3. Three phonocardiograms taken from the third intercostal space parasternally in 3 patients with pulmonary valve regurgitation. *Top strip*: From an 18-year-old girl with a complex congenital heart disease and documented pulmonary valve stenosis and regurgitation. *Middle strip*: From a 7-year-old boy with pure congenital pulmonary valve regurgitation documented by angiocardiography and intracavitary phonocardiography. Note intensification of the diastolic murmur (*arrow*) during inspiration (*marked by black horizontal lines*). *Bottom strip*: The prolonged high-frequency decrescendo murmur of pulmonary hypertension secondary to a large patent ductus is reproduced for comparison. This murmur maintains a fixed intensity in both phases of respiration.

and those of a fixed cardiac output, namely effort dyspnea fatigue, and exertional syncope are the outstanding features.

The usefulness and simplicity of intracardiac phonocardiography in localizing the murmur at the pulmonary valve as pointed out previously[14] have been confirmed. It is to be emphasized further that the phonocardiographic catheter records the murmur of pulmonary valve regurgitation most satisfactorily in the outflow tract of the right ventricle, and therefore does not interfere with the function of the valve. In the other two special techniques of dye dilution and selective angiocardiography a catheter is left within the pulmonary valve and could theoretically prevent the cusps from approximating and thus create spurious regurgitation. It must be stressed however that this phenomenon has rarely been observed in hundreds of pulmonary angiographies performed in our laboratory.

The characteristics of the murmur of the nonhypertensive organic pulmonary valve regurgitation first described by Osler and recounted by Hirschfelder[4] make differentiation between this and the Graham Steell murmur possible. Thus the onset of a murmur a few hundredths of a second after the pulmonary component of the second sound, the short duration, the crescendo-decrescendo configuration, the low frequency components and the circumscribed distribution in the organic valve lesion contrast with the early onset immediately after P, long duration, decrescendo configuration, uniform high frequency structure and the relatively wider distribution of the Graham Steell murmur. The murmur of organic pulmonary valve regurgitation is the same regardless of whether the valve lesion is congenital or acquired (Fig. 8). The behavior of the murmur in relation to respiration is quite characteristic with at least one grade increase on inspiration in the nonhypertensive, organic variety. The Graham Steell murmur on the other hand does not vary with respiration because the right ventricular stroke volume is fixed (Fig. 8).

The pathogenesis of this lesion is of particular interest because of the unique circumstances involved. Although bacterial involvement of the pulmonary valve was



Fig. 9. See text.

relatively common in the course of gonococcal and pneumococcal septicemias in the preantibiotic era it has been extremely rare in the past two decades. It is possible that the low pressure to which the cusps of the pulmonary valve are exposed (the pulmonary arterial diastolic pressure) can explain the relative immunity of this valve to bacterial invasion unless the organism is overwhelmingly virulent. The cases of staphylococcal invasion of the pulmonary valve certainly fall into this latter category. It must be pointed out however that the modern surgical attack on the congenitally stenotic pulmonary valve and the resultant injury may change the picture and bring about a new surge of infectious pulmonary valvulitis with regurgitation.[1]

Summary

Two cases of pulmonary valve regurgitation secondary to right-sided staphylococcal endocarditis in heroin addicts are presented and the characteristic features of the diastolic murmur are described. Intracardiac phonocardiography localizes the murmur at the pulmonary valve and is the simplest most reliable method for documentation of the lesion.

Addendum

Since preparation of this manuscript another case of staphylococcal endocarditis secondary to heroin addiction with pathologic proof of involvement of the pulmonary valve has been observed. In this 50-year-old heroin addict, a severe endocarditis unresponsive to all appropriate antibiotics developed and caused death within 6 weeks. Multiple septic pulmonary emboli with the formation of abscesses occurred (Fig. 9,A). Postmortem examination revealed exuberant vegetations on all three leaflets of the tricuspid valve (Fig. 9,B *white arrows*) and one of the cusps of the pulmonary valve (Fig. 9,B *black arrow*). No murmurs were heard at any time during life.

REFERENCES

1. Bain, R. C., Edwards, J. E., Scheifley, C. H. and Geraci, J. E.: Right-sided bacterial endocarditis and endarteritis, Am. J. Med. 24:98, 1958.
2. Barbour, F. A.: Right-sided bacterial endocarditis, Am. J. M. Sc. 240:411, 1960.
3. Edwards, J. E.: Diseases of the valves and pericardium. Edwards, J. E.: Atlas of acquired diseases of the heart and great vessels, Vol. I, Philadelphia, 1961, W. B. Saunders Company, p. 218.
4. Lepeschkin, E.: The relation between the site of valvular involvement in endocarditis and the pressure resting on the valve, Am. J. M. Sc. 224:318, 1952.
5. Newton-Pitt, G.: Right-sided valvular disease. Allbutt, T. C., editor: A system of medicine, London, 1902, The Macmillan Company, p. 3.
6. Thayer, W. S.: Gonorrheal septicemia and endocarditis, Am. J. M. Sc. 130:751, 1905.
7. Goldburgh, H. L., Baer, S. and Lieber, M. M.: Acute bacterial endocarditis of the tricuspid valve, Am. J. M. Sc. 204:319, 1942.
8. Hussey, H. H., Keliher, T. F., Schaefer, B. F. and Walsh, B. J.: Septicemia and bacterial endocarditis resulting from heroin addiction, J.A.M.A. 126:535, 1944.
9. Hussey, H. H. and Katz, S.: Septic pulmonary infarction: report of eight cases, Ann. Int. Med. 22:526, 1945.
10. Hussey, H. H. and Katz, S.: Infections resulting from narcotic addiction: report of 102 cases, Am. J. Med. 9:186, 1950.
11. Olsson, R. A. and Romansky, M. J.: Staphylococcal tricuspid endocarditis in heroin addicts, Ann. Int. Med. 57:755, 1962.
12. Luttgens, W. F.: Endocarditis in "main line" opium addicts: report on eleven cases, Arch. Int. Med. 83:653, 1949.
13. Bayec, W. F., et al.: Localization and estimation of severity of regurgitation flow at the pulmonary and tricuspid valves, Proc. Staff Meet. Mayo Clin. 33:569, 1958.
14. Collins, N. P., Braunwald, E. and Morrow, A. G.: Detection of pulmonic and tricuspid valvular regurgitation by means of indicator dilutions, Circulation 20:561, 1959.
15. Levin, H. S., Runco, V., Wooley, C. F. and Ryan, J. M.: Pulmonic regurgitation following staphylococcal endocarditis. An intracardiac phonocardiographic study, Circulation 30:411, 1964.
16. Barger, A. C., et al.: Relation of valvular lesions and of exercise to auricular pressure, work tolerance and to development of chronic congestive failure in dogs, Am. J. Physiol. 169:384, 1952.
17. Laneve, S. A., Tesu, C. T. and Taguchi, J. T.: Isolated pulmonic valvular regurgitation, Am. J. M. Sc. 244:446, 1962.
18. Hirschfelder, A. D.: Diseases of the heart and aorta, Philadelphia, 1910, J. B. Lippincott Company, p. 390.
19. Liban, P., Iricchio, J. F., Marino, D. J., Deshmukh, M. and Likoff, W.: Staphylococcal endocarditis, Am. Heart J. 59:184, 1960.

Initial myocardial infarction among veterans: Ten year survival

*Owen W. Beard, M.D.**
Harold R. Hipp, M.D.
Morton Robins, M.S.P.H.
Vincent R. Verzolini, A.B.
Little Rock, Ark.

In 1960 we reported on the mortality rate over a 5-year span of 503 patients in 33 selected Veterans Administration Hospitals who had suffered an acute initial transmural myocardial infarction. In order to obtain a significant number of young patients, a disproportionately large sample of patients under 50 years of age was selected. Of the 503 patients, 427 survived for 2 months after the acute infarction. This report presents the 10-year survival experience of these 427 "recovered" patients.

Our recent inquiries uncovered the fact that 136 of the 427 died during the first 5 years instead of 133 as previously reported. Of the 291 who survived for 5 years after their initial infarction, 105 died during the next 5 years, leaving 186 patients alive at the tenth anniversary of their infarction.

A questionnaire was sent to all of the 10-year survivors still alive in February 1963. We know that 37 patients had died between the tenth anniversary of their first infarction and this date. Three patients who were located did not return the questionnaire and no address could be found for 6. The following analysis is based upon the information in the 140 completed questionnaires, and that obtained from the integrated record system of the Veterans Administration.

Mortality findings

Table I shows the rate of death among those patients who recovered from their acute myocardial infarction. Of the 126 patients under 50 years of age at the time of the initial infarction who survived 5 years, 27 died within the second 5-year period. The cumulative 10-year mortality for patients under 50 years of age is 39 per cent. Of the 165 patients over 50 years of age at the time of their initial infarction who survived 5 years, 78 died during the second 5-year period. The cumulative 10-year mortality for patients over 50 years of age is 67 per cent. Fig. 1 shows the difference in 10-year survival between patients under 50 years of age and those older. The mortality rate for each group remains relatively constant over the period, being approximately 5 per cent a year for those under 50 and approximately 10 per cent a year for those over 50. (For a comparison of observed mortality and expected mortality see previous paper.)

From the Department of Medicine, Veterans Administration Hospital, and the University of Arkansas Medical Center, Little Rock, Ark., and the Reports and Statistics Service of the Veterans Administration, Washington, D.C.
Received for publication May 3, 1966.
*Address: Department of Medicine, Veterans Administration Hospital, 300 East Roosevelt Rd., Little Rock, Ark. 72206.

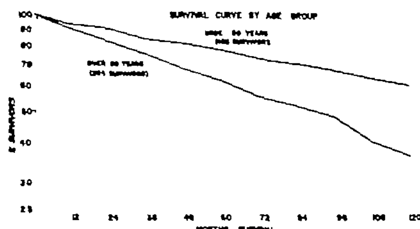


Fig. 1. Difference in 10-year survival between patients under 50 years of age and those over 50 years of age

Table I. Ten year and 5 year mortality rates among recovered patients

Age at time of initial myocardial infarction	10-Year mortality rate among recovered patients*			5-Year mortality rate among recovered patients†		5-9-Year mortality rate among recovered patients‡		
	Patients (number)	Deaths (number)	Rate per 100	Deaths (number)	Rate per 100	Patients (number)	Deaths (number)	Rate per 100
All ages	427	241	56	136	32	291	105	36
Under 50	163	64	39	37	23	126	27	21
50 and over	264	177	67	99	38	165	78	48
Under 30	4	1	§	1	§	3	—	—
30-39	65	27	42	12	18	53	15	28
40-49	94	36	38	24	26	70	12	17
50-59	182	120	66	65	36	117	55	47
60-69	66	41	62	26	39	40	15	38
70 and over	16	16	100	8	50	8	8	100

*Ten-year mortality experience of patients who were alive 2 months after onset.
†Five-year mortality experience of patients who were alive 2 months after onset.
‡Ten-year mortality experience of patients who were alive 5 years after onset.
§Rate not shown because number of patients observed was not large enough to provide valid death rate.

A history of hypertension or angina pectoris preceding the initial infarction was associated with a lower prospect of survival (Table II). However, the mortality rate did not increase for those patients who suffered angina pectoris less than 1 month before the onset of infarction, probably because these symptoms represented the syndrome of premonitory pain. For those 121 patients with a definite history of angina of more than 1 month's duration, the 10-year age-adjusted mortality rate was 67 per cent. For those 154 patients who had no history of angina before their first myocardial infarction, the mortality rate adjusted for age distribution was 55 per cent.

Questionnaire findings

Table III shows the employment status of the patients at the time of the survey. Of 76 who had not reached the retirement age of 65 years, 53 (or 70 per cent) were still employed. Twelve (or 19 per cent) of

Table II Prognostic implications of history of hypertension and history of angina pectoris

	10-Year mortality rate among recovered patients*			5-Year mortality rate among recovered patients†		5-8-Year mortality rate among recovered patients‡		
	Number of patients	Observed rate per 100	Age adjusted rate per 100	Observed rate per 100	Age adjusted rate per 100	Number of patients	Observed rate per 100	Age adjusted rate per 100
History of hypertension	427	56	56	32	32	291	36	36
Yes	77	73	67	44	42	43	51	43
No	305	53	53	30	30	215	33	35
Unknown	45	53	58	[illegible]	28	33	36	40
History of angina								
Yes	233	58	57	35	31	1[illegible]0	37	35
Less than 1 mo.	132	47	47	20	20	105	33	33
1-12 mo.	60	70	70	48	49	31	4[illegible]	40
1-4 yr	34	68	64	47	44	18	39	35
5 yr and over	27	70	66	41	38	16	50	43
Unknown duration	—	—	—	—	—	—	—	—
No	154	33	35	29	30	109	34	37
Unknown history	20	65	63	40	38	12	42	40

*Ten-year mortality experience of patients who were alive 3 months after onset.
†Five-year mortality experience of patients who were alive 3 months after onset.
‡Five-year mortality experience of patients who were alive 5 years after onset.

Table III Employment status by age of 10-year survivors

Employment status	Total	Age at time of survey (1963)			
		Under 65		65 and over	
		Number	Per cent	Number	Per cent
Total	140	76	100.0	64	100.0
Unemployed	75	23	30.3	52	81.3
Employed	65	53	69.7	12	18.7

the 64 survivors who were 65 years of age and over were still employed. Table IV shows the incidence of subsequent heart attacks reported by the patients. These reported events are not verified instances of recurrent myocardial infarction. Approximately one half of the survivors reported no further heart attacks during the 10-year period. Of the 69 patients who had had another heart attack, only 27 or 39 per cent were still employed, whereas of the 71 patients who had not had a second heart attack, 54 per cent were still employed despite the fact that over half of this group was over 65 years of age.

The relationship of symptoms and repeated heart attacks among survivors is shown in Table V. As might be expected, those having had only one attack had fewer cardiovascular symptoms than did those

Table IV. Subsequent heart attacks by age of 10 year survivors

Age (1963)	Total renors responding	Respondents having subsequent heart attack	
		Number	Percentage of total respondent
Total	140	69	49 3
Under 55	39	20	51 3
55-64	37	22	59 5
65 and over	64	27	42 2

Table V. Classification by number of heart attacks and symptoms

Classification of symptoms	All cases		Patients with two or more attacks		Patients with only one attack	
	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
Total	140	100 0	69	100 0	71	100 0
None	22	15 7	8	11 6	14	19 7
Definite angina and shortness of breath	59	42 2	40	58 0	19	26 8
Shortness of breath only*	45	32 1	16	23 2	29	40 8
Definite angina only†	10	7 1	4	5 8	6	8 5
Indefinite angina only†	4	2 9	1	1 4	3	4 2

*Includes patients with presence or absence of angina not reported.
†Includes patients with presence or absence of shortness of breath not reported.

with multiple attacks. Fifty per cent of the respondent survivors had definite angina. An additional 32 per cent reported shortness of breath only. Seventy or one half of the respondents took nitroglycerin either alone or with other cardiovascular drugs. Thirteen patients were taking digitalis or its derivatives. Fifty-seven reported not taking any drugs.

Discussion

There are relatively few reports of 10-year mortality among male patients surviving an initial myocardial infarction and even less information is available on such patients under 50 years of age. However a comparison of some of the published reports shows general agreement when each series is divided by age at onset of infarction into under 50-year and over 50-year age groups. A summary of these reports is given in Table VI.

The reports by Lyle and by Lew[3] were based upon long term follow up of their respective life insurance company employees who had survived 2 months after an acute myocardial infarction. The reports summarized in Table VI cover patients who experienced their myocardial infarctions over a period of approximately three decades. With the exception of the present study which included only those patients who had experienced their first transmural infarction the other reports include patients who had either an intramural or a transmural myocardial infarction. Considering the differences in selection of patients for study and the period of time covered by these reports, the general agreement in long term survival results is all the more remarkable. This agreement suggests that the results do in fact represent the natural history of patients who recovered from an acute myocardial in-

Table VI. Reported 5 year and 10-year survival rates among males who recovered from an acute initial myocardial infarction

Source of data	Source of patients	Recovery period	Dates of entry	Number of recovered patients followed			Per cent surviving 5 yr			Per cent surviving 10 yr		
				All ages	50 yr	50+ yr	All ages	50 yr	50+ yr	All ages	50 yr	50+ yr
Present study	V patients	2 mo.	1950-1952	427	163	264	69	78	63	44	61	33
Cole et al.	Hospital patients	2 mo.	1932 1941	208	62	146	67	79	63	45	65	36
Weiss[3]	Private practice	2 mo.	1940-1945	170	54	116	NA	NA	NA	35	52	28
Lyle[4]	Prudential Life Insurance Co. employees	2 mo.	1933-1960	266	75	191	71	86	65	46	71	36
Lew	Metropolitan Life Insurance Co. employees	2 mo.	1953-1963	95	32	63	77	78	77	49	69	39
Sievers[6]	Hospital patients in Malmo, Sweden	1 mo.	1935-1959	1,039	163	876	59	77	56	39	57	35

NA Not available.

farction, and that the 10-year survivor rate has not changed significantly during the past 30 years.

In addition to this report the only other study which included a large number of patients who were under 50 years of age at the time of their myocardial infarction is that of Sievers. He also found a decreasing survival rate as age at time of infarction increases. In his report, the 10-year survival of recovered patients who were 40 to 49 years of age is similar to that for patients in our study who were under 50 years of age. He noted that patients in the age range of 30 to 39 years appeared to have a worse prognosis than those in the 40-to-49-year group. However he had only a small number of patients in the younger age group. In our series there is little difference between the survival rate for those patients who were 30 to 39 years old (58 per cent 10-year survival) and those who were 40 to 49 years old (62 per cent 10-year survival).

Summary

The report covers an analysis and 10-year review of the history of 427 patients who survived 2 months after their initial transmural myocardial infarction.

Advanced age of the patient, a history of angina pectoris, and a history of hypertension before the initial attack were associated with a higher 10-year mortality rate.

The most favorable prognosis was found in those patients who were under 50 years of age at the time of their original myocardial infarction. In this study, 61 per cent of the patients under 50 years of age who were alive 2 months after the acute infarction lived for 10 years. The corresponding survival rate of those patients over 50 years of age was 33 per cent.

We wish to express our appreciation to the Social Service of the Veterans Administration for their help in obtaining the completed questionnaires.

REFERENCES

1. Beard, O. W., Hipp, H. R., Robins, M., Taylor, J. S., Ebert, R. V., and Beran, L. G.: Initial myocardial infarction among 503 veterans: five year survival, Am. J. Med. 28:871, 1960.
2. Cole, D. R., Singian, E. B., and Katz, L. N.: The long-term prognosis following myocardial infarction and some factors which affect it, Circulation 9:321, 1954.
3. Weiss, M. M.: Ten year prognosis of acute myocardial infarction, Am. J. M. Sc. 231:9, 1956.
4. Lyle, A. M.: Coronary disease as an underwriting problem, T. Soc. of Actuaries 15:314, 1963.
5. Lew, E. A.: Discussion of preceding paper, Tr. Soc. of Actuaries 15:331, 1963.
6. Sievers, J.: Myocardial infarction: clinical features and outcome in three thousand thirty-six cases, Acta Med. Scandinav. Suppl. 406 173:1+, 1964.

Clinical findings in acquired aortic valve stenosis: Effect of disease of other valves

Thomas T. Schattenberg, M.D.
Jack L. Titus, M.D.
Thomas W. Parkin, M.D.
Rochester, Minn.

The clinical findings in patients with acquired stenosis of the aortic valve are well known, and the fact that abnormalities of cardiac valves in addition to the aortic valve may alter the symptoms and course in these patients is recognized. However, the differences between the clinical findings in patients with isolated aortic stenosis and those in patients with aortic stenosis and involvement of other valves have not been studied widely. Therefore, the clinical features of both types were reviewed in a group of patients in whom anatomic confirmation of the valvular lesions was established either at operation or at autopsy.

Material and methods

Two hundred and seven patients with acquired stenosis of the aortic valve who were more than 15 years old underwent operation at the Mayo Clinic through June 30, 1962.† Thirty-five (17 per cent) of these patients had disease of one or more valves in addition to the aortic valve (27 patients had involvement of the aortic and mitral valves, and 8 had involvement of the aortic, mitral, and tricuspid valves). The clinical histories, electrocardiograms, cardiac catheterization data, and operative protocols of all 207 patients were reviewed.

Results

Distributions by age and sex. In men the peak incidences for both isolated and multiple valve diseases occurred in the sixth decade (Table I). In women isolated aortic valve disease was most common in the sixth decade, whereas multiple valve disease was most common in the fifth decade. Isolated aortic valve disease was four times as common in men as in women, but there was no significant sex difference for multivalve disease. In the entire series, men predominated by a ratio of 2.9:1.

Presenting symptoms and signs. The incidences of certain signs and symptoms are shown in Table II. A history of angina pectoris or a previous myocardial infarction was noted in 53 per cent of the women and 72 per cent of the men in the entire group.

Electrocardiographic findings. Ten patients had a mean QRS axis in the frontal plane ($\hat{A}_{QRS}$) of +90 degrees or greater; 5 of these had involvement of multiple

Received for publication May 6, 1966.
*Section of Medicine, Mayo Clinic and Mayo Foundation.
**Section of Experimental and Anatomic Pathology, Mayo Clinic and Mayo Foundation.
†We wish [illegible] thank Dr. J. [illegible] Kirklin and Dr. D. C. McGoon for permission [illegible] use clinical data from their cases.

Table I. Age and sex distributions of patients with acquired stenosis of the aortic valve

Age range (yr)	Total number in study		Number with isolated aortic valve disease		Number with multiple valve disease	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
15-19	2	2	2	2	0	0
20-29	7	2	6	0	1	2
30-39	19	10	15	6	4	4
40-49	46	16	42	7	4	9
50-59	72	19	65	16	7	3
60 and over	8	4	8	3	0	1
Total	154	53	138	34	16	19

Table II. Incidence of certain symptoms and signs in patients with acquired stenosis of the aortic valve

Symptom or sign	Incidence in entire series of 207	Incidence in 172 with isolated aortic valve disease	Incidence in 35 with multiple valve disease
Angina or previous infarct	139 (67)*	122 (71)	17 (49)
Exertional syncope	61 (29)	55 (32)	6 (17)
Exertional dyspnea	185 (89)	154 (90)	31 (89)
Orthopnea or edema	96 (46)	70 (41)	26 (74)
Arrhythmia by history or on ECG	73 (35)	55 (33)	18 (51)
Aortic systolic thrill	112 (54)	103 (60)	9 (26)
Aortic insufficiency	142 (69)	118 (69)	24 (69)
Bicuspid aortic valve†	42 (20)	40 (23)	2 (6)

*All numbers in parentheses are per cent.
†This anatomic finding is included in the table for convenience.

Table III. Electrocardiographic findings in patients with acquired stenosis of the aortic valve

ECG finding	Incidence in entire series of 207	Incidence in 172 with isolated aortic valve disease	Incidence in 35 with multiple valve disease
$Â_{QRS}$ at 0 degree or less	67 (32)*	60 (35	7 (20
LVH (see text)	89 (43)	80 (47	9 (26)
Strain T pattern	160 (77)	137 (80)	23 ([illegible]
Intraventricular conduction delay	25 (12)	21 (1)	4 (11)
$Â_{QRS}$ at +90 degrees or more	10 (5)	5 (3	5 (14

*All numbers in parentheses are per cent.

Table IV. Transaortic valve peak systolic pressure gradients in patients with acquired stenosis of the aortic valve

Type of valvular involvement	Peak systolic gradient across aortic valve		
	50 mm. Hg or less (28 patients)	50 to 99 mm. Hg (105 patients)	100 mm. Hg or more (55 patients)
Isolated aortic valve disease (number)	22	82	51
Multiple involvement (number)	6	23	4

valves (Table III). Sixty of the patients with isolated aortic valve disease had an $\hat{A}_{QRS}$ axis of 0 degree or less and 7 with multiple involvement had such a finding. Aortic insufficiency was found on physical examination or at operation in 78 per cent of the patients with an $\hat{A}_{QRS}$ of 0 degree or less. An electrocardiographic diagnosis of left ventricular hypertrophy (LVH) was made only when the sum of the voltages of S in Lead V and R in Lead V was 45 mm. or greater. Strain T pattern was defined as depression of the S-T segment with the initial limb of the inverted T wave longer than the final limb, both limbs being convex upward. Delayed intraventricular conduction was defined as QRS duration of 0.12 second or more.

Transaortic valve pressure gradients. Peak systolic pressure gradients across the aortic valve were measured in 155 patients with isolated aortic valve disease and in 33 patients with multiple valve disease (Table IV). Gradients in excess of 100 mm. Hg were observed in 33 per cent of the former group and in 12 per cent of the latter.

Aortic valve calcification. Sixteen (46 per cent) of those with multiple valve disease and 126 (73 per cent) of those with isolated aortic valve disease had calcification of the aortic valve at the time of fluoroscopy.

Discussion

In this study, the age range of patients with multiple valve disease was similar to that of those with isolated aortic valve disease. However, the symptoms of the patients with multiple valve disease resembled more those of mitral disease than those of pure aortic stenosis. Congestive failure and cardiac arrhythmias were more common in the group with multiple involvement, whereas angina pectoris and exertional syncope were more common in the group with isolated aortic valve disease.

This difference in symptom complexes in the two groups might be expected because of the recognized protective effects of mitral stenosis on left ventricular function. It has been observed previously[2-4] that the symptoms of mitral stenosis predominate in patients with both mitral and aortic stenoses.

Exertional syncope has been reported in none[8] to 16 per cent[4] of patients operated on for aortic and mitral stenoses, whereas angina pectoris has been present in 12 to 23 per cent[8] of such patients. In our series, syncope was found in 17 per cent and angina pectoris in 49 per cent. This difference between reported incidences and those observed by us might be due in part to the fact that we included patients with mitral insufficiency and tricuspid valve disease as well as mitral stenosis in the group with multiple involvement. However, in all cases aortic stenosis was the dominant lesion, both clinically and at operation.

The finding that 12 per cent of the patients with multiple valve disease had peak transaortic pressure gradients greater than 100 mm. Hg is in contrast to the findings of Morrow and associates.[4] Honey[8] found that 12 per cent of patients with aortic and mitral stenoses had transaortic gradients greater than 75 mm. Hg. Honey emphasized the proportionate relationship of the aortic valve gradient to the cardiac output and noted that the cardiac indices

in his series of 35 patients with aortic and mitral stenoses were lower than those observed by Hancock and Fleming[7] in patients with isolated aortic stenosis. Honey thought that these differences in cardiac outputs accounted for the lower transaortic pressure gradients the rarity of more than slight electrocardiographic evidence of LVH and the infrequency of angina pectoris in his group of patients. Although his postulate—that the existence of mitral stenosis with its low resting cardiac output in association with aortic stenosis may be responsible for initiating regional shunting mechanisms which prevent exertional syncope—has not been proved It remains an attractive concept to explain the less frequent occurrence of this symptom in multiple valve disease.

Several authors[1,4,9] have warned that apparently "insignificant" aortic valve disease may become hemodynamically important after correction of coexistent mitral valve disease. For example the sudden relief of mitral stenosis apparently placed an intolerable burden on the left ventricle in 3 patients with aortic and mitral stenoses reported by Uricchio and Likoff On the other hand the minor degrees of mitral insufficiency which may result from mitral commissurotomy can be augmented by the increased left ventricular systolic pressure present if there is associated aortic stenosis. Therefore evaluation of both valves at the time of surgical repair appears to be necessary

Summary

The symptoms, physical findings electrocardiographic features, and transaortic pressure gradients in a group of 172 patients with isolated aortic valve stenosis were compared with similar data from a group of 35 patients with predominant aortic valve stenosis and coexistent abnormalities of either the mitral or tricuspid valve, or of both The incidences of angina pectoris exertional syncope palpable aortic systolic thrills left ventricular hypertrophy left ventricular strain pattern and marked increase in the transaortic pressure gradient were lower in the group with multiple valve involvement, whereas congestive failure and arrhythmias were more common.

REFERENCES

1 Bailey C. P Bolton, H. E., Nichols, H. T Jamison, W. L., and Litwak, R. S. The surgical treatment of aortic stenosis, J Thoracic Surg 31:375 1956.
2. Honey M Clinical and haemodynamic observations on combined mitral and aortic stenosis, Brit. Heart J 23:545 1961.
3 Katznelson, G., Jreissaty R. M., Levinson, G. E., Stein, S W and Abelmann, W H Combined aortic and mitral stenosis A clinical and physiological study Am. J Med. 29:242, 1960.
4. Morrow A. G., A e, W C., and Braunwald, E. Combined mitral and ortic stenosis, Brit Heart J 24:606, 1962.
5. Uricchio, J F Goldberg, H Sinah, K. P and Likoff W Combined mitral and aortic stenosis Clinical and physiologic features and results of surgery Am. J Cardiol. 1:479 1959
6. Uricchio, J F and Likoff W Effect of mitral commissurotomy on coexisting aortic-valve lesions, New England J Med. 256 199 1957
7 Hancock, E. W and Fleming, P R. Aortic stenosis, Quart. J Med. 29:209 1960.
8. Reid, J M., Stevenson, J G., Barclay R. S and Welsh, T M Combined aortic and mitral stenosis, Brit. Heart J 24:509 1962.
9 Starr A., Edwards, M. L., McCord, C. W Wood, J Herr R., and Griswold, H E. Multiple-valve replacement, Circulation (Suppl. 1) 29:30, 1964.

Experimental and laboratory reports

Hemodynamic effects of angiotensin during surgical anesthesia

*John M Wallace M D**
*Geraldo Lopez M D***
*Rodolfo Malo-Camacho M D***
*Joe A deLeon M D***
Joseph P Walker M D
Thomas D Kirksey M.D
John R Derrick M.D
Galveston Tex

The use of angiotensin in hypotensive states remains controversial despite clinical reports of satisfactory results.[1] One reason for this is the adverse hemodynamic effects of the drug in normal subjects and in certain normotensive patients which if applicable during hypotension would not lead one to expect favorable results. These effects include lowering the cardiac output slowing the heart rate decreasing the stroke volume and increasing the peripheral resistance.[7, 13] Another reason is that in shock the effects of angiotensin are still uncertain Udhoji and Weil[14] suggested that angiotensin was inferior to other pressor agents but Cohn and Luria considered it to be approximately as effective as norepinephrine except in patients with heart failure.

A major problem is the variation in patients responsiveness to angiotensin a fact which makes comparisons of different data difficult. For example the pressor response may vary depending on the blood pressure history[15] the state of fluid balance or recent diuretic history[16] The presence of cirrhosis,[7] aortic insufficiency[12] or heart failure[1] is important. Sympathetic nervous activity also plays a role in determining its effects.[10, 21] Thus it is not surprising that indications for the clinical use of this drug remain controversial and difficult to crystallize

Surgical anesthesia is another clinical condition in which hypotension is often present and pressor drugs are frequently used Here again satisfactory clinical results have been reported with angiotensin during surgery[4] but hemodynamic observations have not been reported The present study was carried out to determine whether the hemodynamic effects of angiotensin are altered by anesthesia in an effort to clarify its use during surgery

Materials and methods

Ten patients were studied immediately prior to surgery (Table I) All were on the Cardiovascular Surgery Service but were otherwise unselected In every patient

From the Departments of Medicine Anesthesiology and Surgery University of Texas Medical Branch, Galveston, Tex.
Supported in part by grant from the Southeast Texas Heart Association, and part by United States Public Health Service Training Grant No 5T1 HE 5347-03 from the National Heart Institute.
Received for publication May 5, 1966.
Address Cardiopulmonary Laboratories, University of Texas Medical Branch, Galveston, Tex 77550.
**Work performed during the tenure of United States Public Health Service Postdoctorate Fellowships.

anesthesia was induced with sodium Pentothal followed by succinylcholine chloride endotracheal intubation halothane-ether and nitrous oxide and oxygen Four of the 10 patients were given atropine 0 2 or 0 3 mg intravenously prior to the injection of Pentothal

Studies were carried out in the anesthesia suite during a 2 hour period before the patient was moved to the operating room. A catheter was threaded into the superior vena cava and the ECG brachial arterial pressure and superior vena caval pressure were recorded continuously Indocyanine green was injected into the superior vena cava to obtain cardiac output curves which were recorded by withdrawal of blood from the brachial artery through a Colson densitometer Prior to anesthesia data were collected before and at the end of a 10-minute period of infusion of angiotensin. Fifteen minutes after the infusion was stopped anesthesia was begun. After surgical anesthesia had been achieved the anesthetist made an effort to maintain an even state cardiac output was determined the infusion was repeated exactly as given previously and the cardiac output was measured again Some patients were respired by the anesthesiologist in which case the injections of indocyanine green were made at the end of an expiration and no further respirations were made until the completion of the dye curve.

Angiotensin amide was given intravenously with a Harvard infusion pump at the rate of 1.5 μg per minute to 7 of the 10 patients. Patient R M who had recently completed a vigorous course of diuretic therapy for severe congestive failure was insensitive to angiotensin and required an infusion of 6.0 μg per minute to raise the mean pressure 27 mm Hg Patient K. G who had essential hypertension[*] was hypersensitive to the drug and was given only 0 75 μg per minute Even this amount increased the mean pressure 64 mm Hg Patient P W was given 3 0 μg per minute.

Results

Table II presents data obtained in 10 patients after 10 minutes of infusion of angiotensin before and during anesthesia Table III presents data obtained in 5 of the patients in whom the infusion was continued for 20 minutes during anesthesia, and in whom cardiac output was measured at both 10 and 20 minutes.

Cardiac rhythm All patients were in normal sinus rhythm prior to anesthesia. During induction 5 patients developed a nodal rhythm and 2 developed pulsus alternans. In one of these patients M B who was hypertensive pulsus alternans was also present intermittently during the infusion of angiotensin. Otherwise the abnormalities of rhythm subsided after surgical anesthesia had been achieved and did not return with angiotensin.

Heart rate Before anesthesia the heart rate of 84.3 ± 15 4 was decreased by angiotensin to 75 2 ± 14 6 $p < 01$ The resting heart rate was little changed by anesthesia or by the administration of angiotensin during anesthesia.

Arterial pressure Before anesthesia, the mean arterial pressure of 89 1 ± 18.8 mm Hg was increased by angiotensin to 125 1 ± 33 6 mm. Hg an average rise of 36.0 mm Hg Anesthesia lowered the mean arterial pressure to 63.5 ± 15 7 mm Hg and the pressure was increased to only 84.3 ± 17 3 by angiotensin This increase of 20 8 mm Hg was less than the increase of 36 0 mm Hg prior to anesthesia $p < 025$

Cardiac output Before anesthesia angiotensin lowered the cardiac output in 8 of the 10 patients, the mean value having fallen from 4 96 ± 1.38 to 4.45 ± 1 47 L. per minute, $p = 01$ This is a change of −12.0 ± 12.2 per cent. Anesthesia lowered the resting cardiac output to 3 97 ± 1 02 L. per minute $p < 01$ and angiotensin further lowered this output in 6 of the 10 patients, but in only one of these Patient K.G was the decrease as great as or greater than in the awake state The change due to angiotensin was not significant

In Patient K.G the mean pressure dropped to 34 mm Hg with anesthesia at which time the cardiac-output dye curve

*Hypertension, Clin.

*† 10 other patients with heart disease duplicate serial cardiac outputs, measured within 5 minutes of each other, differed by 4 94 ± 3 33 per cent; and in 30 similar determinations in the present patients under the various conditions of this study the difference was .81 ± [illegible] per cent.

Experimental and laboratory reports

Hemodynamic effects of angiotensin during surgical anesthesia

John M. Wallace, M.D.
*Gerardo Lopez, M.D.***
Rodolfo Mulo-Camacho, M.D.
Joe A. deLeon, M.D.
Joseph P. Walker, M.D.
Thomas D. Kirksey, M.D.
John R. Derrick, M.D.
Galveston, Tex.

The use of angiotensin in hypotensive states remains controversial despite clinical reports of satisfactory results.[1] One reason for this is the adverse hemodynamic effects of the drug in normal subjects and in certain normotensive patients which, if applicable during hypotension, would not lead one to expect favorable results. These effects include lowering the cardiac output, slowing the heart rate, decreasing the stroke volume, and increasing the peripheral resistance.[7-13] Another reason is that in shock the effects of angiotensin are still uncertain. Udhoji and Weil[14] suggested that angiotensin was inferior to other pressor agents, but Cohn and Luria considered it to be approximately as effective as norepinephrine except in patients with heart failure.

A major problem is the variation in patients' responsiveness to angiotensin, a fact which makes comparisons of different data difficult. For example, the pressor response may vary depending on the blood pressure history,[15] the state of fluid balance,[9] or recent diuretic history.[16] The presence of cirrhosis,[17] aortic insufficiency,[18] or heart failure[1] is important. Sympathetic nervous activity also plays a role in determining its effects.[19,20] Thus it is not surprising that indications for the clinical use of this drug remain controversial and difficult to crystallize.

Surgical anesthesia is another clinical condition in which hypotension is often present and pressor drugs are frequently used. Here again satisfactory clinical results have been reported with angiotensin during surgery,[2] but hemodynamic observations have not been reported. The present study was carried out to determine whether the hemodynamic effects of angiotensin are altered by anesthesia in an effort to clarify its use during surgery.

Materials and methods

Ten patients were studied immediately prior to surgery (Table I). All were on the Cardiovascular Surgery Service but were otherwise unselected. In every patient

From the Departments of Medicine, Anesthesiology, and Surgery, University of Texas Medical Branch, Galveston, Tex.
Supported in part by a grant from the Southeast Texas Heart Association, and in part by United States Public Health Service Training Grant No. 5T1 HE 5417-03 from the National Heart Institute.
Received for publication May 5, 1964.
Address: Cardiopulmonary Laboratories, University of Texas Medical Branch, Galveston, Tex. 77550.
**Work performed during the tenure of a United States Public Health Service Postdoctorate Fellowship.

Drugs	*Edema*	*Atropine*	*Other premedication*	*Rate of infusion of angiotensin II*	
				μg/min	*μg/70 Kg/min*
Gantrisin	N	0 3 mg	N	3 0	7 78
Digitalis and hydrochlorothiazide	Recent	0 2 mg.	Y	6 0	7 06
Neothalidine	N	N	No	1 5	2 22
Digitalis and potassium	N	0 2 mg	No	1 5	2 34
Potassium iodide and tetracycline	N	N	No	1 5	1 40
None	N	No	Yes	1 5	1 64
None	N	N	N	1 5	1 71
None	No	No	N	1 5	1 64
Tetracycline and Lincocin	N	0 3 mg	N	0 75	0 84
Penicillin and ferrous sulf te	No	N	N	1 5	1 75

adverse were less so under anesthesia. Only the stroke volume, which fell slightly during anesthesia, was unfavorably affected by the 10-minute infusion and this change was not sufficient to influence cardiac output significantly. In the 2 patients in whom hypotension during anesthesia became alarming (H I and K.G.) angiotensin clearly improved the hemodynamic state, and in 5 anesthetized patients in whom it was administered for longer than 10 minutes there was a definite tendency toward improvement in both the cardiac output and stroke volume without a further rise in peripheral resistance. These results suggest that when hypotension accompanies halothane anesthesia, angiotensin has a beneficial hemodynamic effect when used as it was here in low dosage for short periods of time. Observations were not extended to prolonged infusions of angiotensin or to a comparison with norepinephrine.

The anesthetic agents employed in these patients, the major one being halothane, caused a fall in mean arterial pressure, cardiac output, and stroke volume. Peripheral resistance and heart rate were little affected. These changes are known to occur with halothane[22] and have been ascribed in part to a central depression of the sympathetic nervous system.[23-27] This may partially explain the diminished effect of angiotensin on the arterial pressure and peripheral resistance during anesthesia, since a portion of its pressor effect appears to depend upon stimulation of central sympathetic elements.[23-27] In addition, angiotensin is inotropic to heart muscle in vitro[28,29] but this effect is not apparent in man, perhaps because it is overwhelmed by the usual marked rise in arteriolar resistance. Diminution of the latter effect by a reduction in central sympathetic activity might establish a more favorable balance between these opposing effects of the drug. These considerations emphasize the possibility that the findings of this study might not apply to an anesthetic agent which does not reduce sympathetic activity.

In this study the patients were anesthetized but had not yet undergone surgery. Whether surgery itself, particularly if shock occurred, would have changed the response is unknown. In unanesthetized patients in shock large doses of angiotensin or norepinephrine are required to restore, even partially, the blood pressure and cardiac output.[4] The effect of anesthesia and particularly the effects of reduced sympathetic activity have not been determined under these circumstances. However, the possibility that reduced sympathetic activity might be beneficial in shock was emphasized by Eaton[32]

Table II Values obtained before (C) and after angiotensin (AII) given for 10 minutes to awake

Patient	HR (Awake)		HR (Anesthetized)		SVC (Awake)	
	C	AII	C	AII	C	AII
P W	74	68	87	80	1 0	0 0
R M	107	81	117	108	3 0	3 0
H I	90	82	90	96	1 0	1 7
D P	93	84	81	85	0 6	0 3
O M	93	94	102	102	—	—
P M	63	65	58	59	1 0	7 0
M B	9	89	84	87	0 0	3 0
L B	68	49	70	73	3 0	7 0
K G	96	83	69	69	1 0	1 0
O P	65	57	68	69	1 0	3 2
Mean	84 3	75 2	82 6	82 8	1 3	2 9
S D	±15 4	±14 6	±17 6	±15 8	±1 0	±2 6
Δ	−9 1		+0 2		+1 6	
p value	< 01		NS		NS	

Patient	CO (Anesthetized)		CI (Awake)		CI (Anesthetized)	
	C	AII	C	AII	C	AII
P W	3 94	3 68	2 85	1 92	2 51	2 34
R M	2 51	2 39	1 59	1 13	1 48	1 41
H I	2 54	2 93	2 06	1 99	1 71	1 98
D P	3 98	2 98	3 33	2 83	2 34	1 73
O M	4 42	4 63	2 98	3 07	2 51	2 63
P M	3 95	3 66	3 42	3 44	2 31	2 13
M B	3 66	3 79	3 07	2 89	2 27	2 35
L B	5 32	5 12	3 40	2 93	3 43	3 30
K G	3 67	2 94	2 80	2 65	2 29	1 84
O P	5 67	5 21	4 41	4 13	3 34	3 06
Mean	3 97	3 73	3 0	2 7	2 4	2 3
S.D	±1 0	±1 02	±0 78	±0 97	±0 61	±0 60
Δ	−0 24		−0 3		−0 1	
p value	NS		< 01		NS	

HR, Heart rate. *SVC*, Pressure (mm Hg) in superior vena cava. *BA*, Mean pressure in brachial artery. *CO*, Cardiac output in liters ... resistance in dynes sec cm.⁻⁵ Statistical analysis was performed by the comparison of paired data, each subject serving as his own control.

in 1957 and Johnstone[44] considered the antisympathetic properties of halothane to be beneficial in shock. Therefore the hemodynamic effects of angiotensin and other pressor agents might be more favorable in shock which arises during halothane anesthesia than otherwise.

The important matter of blood flow in organs was unexamined in the present study However it is of interest to note that hydralazine which has a central blocking effect on sympathetic activity reduces the renal vascular constriction produced by angiotensin in dogs.[45] Whether the central action of halothane would produce a similar result has not been reported

and anesthetized patients

SVC (Anesthetized) C	SVC (Anesthetized) AII	BA (Awake) C	BA (Awake) AII	BA (Anesthetized) C	BA (Anesthetized) AII	CO (Awake) C	CO (Awake) AII
0 0	1 0	92	130	64	89	4 74	3 03
7 0	7 7	84	111	83	105	2 70	1 92
8 0	9 0	60	109	39	59	3 06	2 96
3 0	4 0	91	108	59	84	5 76	4 82
—	—	96	119	76	78	5 24	5 41
8 0	3 0	78	101	53	63	5 85	5 89
5 0	0 0	112	190	90	114	4 95	4 67
4 0	—	93	133	66	80	5 37	4 55
1 0	−1 0	92	156	30	96	4 49	4 25
8 5	3 2	73	94	55	75	7 50	[illegible]
4 4	3 4	89 1	125 0	63 5	84 8	4 96	4 45
±2 9	±3 7	±18 8	±33 6	±15 7	±17 3	±1 38	±1 47
−1 0		+35 9		+20 8		−0 51	
NS		< 01		< 001		< 01	

SV (Awake) C	SV (Awake) AII	SV (Anesthetized) C	SV (Anesthetized) AII	Syst Resist. (Awake) C	Syst Resist. (Awake) AII	Syst. Resist. (Anesthetized) C	Syst. Resist. (Anesthetized) AII
64 3	44 6	45 4	45 8	1 552	3 432	1 299	1 934
25 2	23 7	21 4	22 1	2 488	4 625	2 645	3 514
34 0	36 1	28 2	30 5	1 563	2 945	1 228	1 611
58 7	57 4	49 1	35 0	1 263	1 79"	1 185	2 255
30 9	3 8	43 4	45 0	1 465	1 759	1 375	1 347
86 0	90 1	67 4	61 5	1 066	1 371	1 073	1 377
33 8	52 4	43 3	43 6	2 133	3 240	1 967	2 406
78 1	75 8	75 1	69 9	1 411	2 333	992	1 250
46 7	51 1	53 1	42 6	1 639	2 936	1 089	2 611
115 3	123 2	83 4	75 4	778	1 071	776	1 151
59 3	58 7	31 0	47 1	1 536	2 531	1 362	1 946
±27 9	±29 9	±19 6	±17 3	±490	±1 050	±548	±746
−0 5		−3 9		+1 015		+584	
NS		< 05		< 001		< 003	

per minute. CI Cardiac index in liters per minute per square meter SV Stroke volume Syst Resist Total systemic vascular [illegible]. Group means and standard deviations (S D) are also given. NS, Not statistically significant. ≥ 45 Δ [illegible] of group

Summary

The effects of a 10 to 20-minute infusion of angiotensin II on the cardiac output and arterial pressure were studied in 10 patients anesthetized with halothane-ether Cardiac output did not fall significantly and peripheral resistance rose less than it did before anesthesia. In 2 seriously hypotensive patients angiotensin markedly increased the cardiac output and in 4 of 5 patients given the infusion for 20 minutes, cardiac output, but not peripheral resistance was higher at 20 than at 10 minutes. These observations suggest that when hypotension accompanies halothane anesthesia angiotensin has a beneficial

Table III Effects of continuing the infusion of angiotensin for 20 minutes in anesthetized

Patient	Unanesthetized patients									
	No angiotensin					No angiotensin				
	HR	MP	CO	SV	SR	HR	MP	CO	SV	SR
H I	90	60	3 06	34 1	1 570	90	39	2 54	28 2	1 228
D P	93	91	5 76	58 7	1 280	81	59	3 98	49 2	1 186
M B	92	132	4 95	53 8	2 138	84	90	3 66	43 5	1 967
L B	68	93	5 27	78 1	1 420	70	66	5 32	75 7	992
O P	65	73	7 50	115 9	780	68	55	5 67	83 4	776
Mean	82	90	5 31	68 1	1 438	79	56	4 23	56 0	1 230

HR Heart rate MP Mean pressure CO Cardiac output SV Stroke volume SR Systemic resistance.

hemodynamic effect when used as it was here in low dosage for short periods of time.

REFERENCES

1 Del Greco, F and Johnson, D C. Clinical experience with angiotensin II in the treatment of shock, J.A.M.A. 178:994 1961
2 Derrick, J R Anderson, J R and Roland, B H Adjunctive use of a biologic pressor agent, angiotensin, in management of shock, Circulation 25:263 1962
3 Wedeen, R and Zucker G Angiotensin II in treatment of shock, Am. J Cardiol. 11:82, 1963.
4. Arens, J F and Adriani, J The use of angiotensin as an adjunctive agent to correct hypotensive states during anesthesia, Anesth. Analg (Cleveland) 42:536, 1963
5 Nassif, A.C Nolan, T R., and Corcoran, A.C Angiotensin II in treatment of hypotensive states, J.A.M.A 183 751 1963.
6. Beanlands, D S and Gunton, R W Angiotensin II in the treatment of shock following myocardial infarction, Am J Cardiol. 14:370, 1964.
7 Sancetta, S. M General and pulmonary hemodynamic effects of pure decapeptide angiotensin in normotensive man, Circulation Res. 8:616, 1960.
8. Finnerty F A., J Massaro, G D Chupkovich, V and Tuckman, J Evaluation of the pressor cardiac, and renal hemodynamic properties of angiotensin II in man, Circulation Res. 9:256 1961
9 Yu, P N Luria, M N Finlayson J K., Stanfield C. A., Constantine, H and Flatley F J The effects of angiotensin on pulmonary circulation and ventricular function Circulation 24 1326 1961
10. Johnson, W P., and Bruce, R. A. Hemodynamic and metabolic effects of angiotensin II during rest and exercise normal healthy subjects, Am Heart J 63:212, 1962.
11 Cumming G R Acute hemodynamic effects of angiotensin II Canad M A J 88:827 1963
12. Segel, N Bayley T J and Bishop, J M The circulatory effects of angiotensin in rheumatic heart disease, Clin. Sc. 27 77 1964.
13. Udhoji V N and Weil, M H Circulatory effects of angiotensin, levarterenol and metaminol in the treatment of shock New England J Med. 270:501 1964.
14 Cohn, J N and Luria, M H Studies in clinical shock and hypotension. II. Hemodynamic effects of norepinephrine and angiotensin, J Clin. Invest. 44 1494 1965.
15 Kaplan N M and Silah J G. Effect of angiotensin II on blood pressure in humans with hypertensive disease, J Clin. Invest. 43:659 1964
16. Laragh, J H., Cannon, P J Bentzel, C. J Sicinski A. M and Meltzer J I Angiotensin II norepinephrine, and renal transport of electrolytes and water in normal man and in cirrhosis with ascites, J Clin. Invest. 42 1179 1963.
17 Ames, R. P Borkowsky A. J Sicinski, A. M., and Laragh, J H Prolonged infusions of angiotensin II and norepinephrine and blood pressure, electrolyte balance and aldosterone and cortisol secretion in normal man and in cirrhosis with ascites, J Clin Invest. 44 1171 1965.
18. Zimmerman, B G Effect of acute sympathectomy on response to angiotensin and norepinephrine, Circulation Res. 11 780, 1962.
19 McCubbin J W and Page, L H. Renal pressor system and neurogenic control of arterial pressure, Circulation Res. 12:553 1963.
20. Benelli, G Della Bella, D and Gandini, A. Angiotensin and peripheral sympathetic nerve activity Brit. J Pharmacol. 22:211 1964

patients

Patients under anesthesia

Angiotensin 10 min.					Angiotensin 20 min				
HR	*MP*	*CO*	*SV*	*SR*	*HR*	*MP*	*CO*	*SV*	*SR*
87	59	2 93	33 7	1 611	83	80	3 70	44 5	1 730
87	84	2 98	34 2	2 255	85	84	4 10	48 5	1 539
87	119	3 79	43 6	2 565	82	113	3 55	43 2	2 547
73	80	5 12	69 9	1 250	78	104	5 99	76 7	1 389
64	75	5 21	75 4	1 152	63	74	6 62	105 1	894
80	83	4 01	51 4	1 767	78	91	4 79	63 6	1 640

21 McGiff, J C., and Fasy T M The relationship of the renal vascular activity of angiotensin II to the autonomic nervous system, J Clin. Invest. 44 1911 1965
22. Greisheimer E. M The circulatory effects of anesthesia, in Handbook of physiology Circulation, Vol. III pp. 2490- 491 (publication of the American Physiological Society) Baltimore, 1965, Williams & Wilkins Co.
23 Price, H L., Jr Linde, H. W Jones, R E Black, G. W and Price, M. L. Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics Anesthesiology 20:563 1959
24 Black, G. W and McArdle, L. The effects of halothane on the peripheral circulation in man, Brit. J Anaesth. 34:2, 1962
25. Deutsch, S., Linde H W Dripps, R. D and Price H L. Circulatory and respiratory actions of halothane in normal man, Anesthesiology 23:631 1962.
26 Price, H L., Linde, H. W and Morse, H. T Central nervous actions of halothane affecting the systemic circulation, Anesthesiology 24 770 1963.
27 Caffrey J A., Eckstein, J W Hamilton, W K., and Abboud, F M. Forearm venous and arterial responses to halothane and cyclopropane Anesthesiology 26 786, 1965.
28. Bickerton R. K., and Buckley J P Evidence for central mechanism in angiotensin induced hypertension, Proc Soc. Exper Biol. & Med. 106:834, 1961
29 Buckley J P Bickerton, R. K Halliday R. P and Kato, H. Central effects of peptides on the cardiovascular system, Ann. New York Acad. Sc. 104:299 1963.
30 Laverty R. A nervously mediated action of angiotensin in anesthetized rats, J Pharm. & Pharmacol. 15:63 1963.
31. Buckley J P Effects of synthetic angiotensin II on catecholamine levels and biological activity Acta Physiol Scandinav 65:273, 1965.
32. Fowler N O and Holmes, J C. Coronary and myocardial actions of angiotensin, Circulation Res. 14 191 1964.
33. Koch-Weser J Myocardial actions of angiotensin, Circulation Res. 14:337 1964.
34 Koch Weser J Nature of the inotropic action of angiotensin on ventricular myocardium, Circulation Res. 16:230 1965.
35. Paton, W D M Methods and consequences of lowering the blood pressure Ulster M J 26:17 1957
36. Johnstone, M The role of halothane in the prevention of surgical shock, Brit J Anaesthesia 30:435 1958.

The normal closure of the ventricular septum

*Sheila C. Mitchell, M.D., M.P.H.**
*Heinz W. Berendes, M.D.***
*William M. Clark, Jr., M.D.****
Bethesda, Md.

Although experimental proof is lacking, it has generally been conceded that membranous ventricular septal defects are due either to failure of the right and left bulbar ridges to fuse with each other or with the endocardial cushions at horizon XVII (approximately 35 days after conception)[1-4] or to a minor degree of lack of torsion of the primitive cardiac tube at approximately horizon X (some 22 days after conception).[4] Muscular defects are presumably due to excessive trabeculation during formation of the ventricles or to aberrations in the coalescence of the myocardial shells which normally contribute to the formation of the interventricular septum.

In 1960 Evans, Rowe and Keith documented by repeat cardiac catheterization the first case of postnatal closure of an isolated ventricular septal defect. By 1963 13 such cases had been recorded.[6] Since all of these patients survived, the mechanism of closure in them can only be surmised. Three patients[9] without clinical documentation of closure were found to have a membranous ventricular septal defect sealed off by fibrous adhesion of the medial leaflet of the tricuspid valve. Without autopsy proof, closure by fibrous tissue or hypertrophy of muscle bundles has been postulated.[11]

In 1965 Hoffman and Rudolph,[1] reporting on 62 infants with isolated ventricular septal defects, described the case of a 1,250-gram infant with a clinically typical ventricular septal defect at 51 days of age who at 12 weeks of age showed a small ventricular septal defect by cineangiography, and at 15 weeks an entirely normal heart by autopsy. The patient died at home of undetermined cause. Although this in-

From the Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

The Collaborative Study of Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood is supported by the National Institute of Neurological Diseases and Blindness. The following institutions participate: Boston Lying-In Hospital; Brown University; Charity Hospital, New Orleans; Children's Hospital of Buffalo; Children's Hospital of Philadelphia; *Children's Medical Center, Boston; Columbia University; Johns Hopkins University; Medical College of Virginia; New York Medical College; Pennsylvania Hospital; University of Minnesota; University of Oregon; University of Tennessee; Yale University; and the Perinatal Research Branch, N.I.N.D.B. (*Babies born in Boston Lying-In Hospital are followed-up at Children's Medical Center of Boston, and these are treated as one institution; the same rule applies to Pennsylvania Hospital and Children's Hospital of Philadelphia.)

Received for publication May 6, 1966.

*Collaborative Studies Program Area, Geographic Pathology Section, National Heart Institute, National Institutes of Health. Address: National Heart Institute, National Institutes of Health, Bldg. 31, Room 5 A 06, Bethesda, Md. 20014.

**Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health.

***Department of Pediatrics, University of Oregon Medical School, Portland, Ore.

fant was premature the authors did not find among their 13 patients with complete closure a disproportionate number of premature infants. However one third of their cases of ventricular septal defects were in infants with birth weights under 2,500 grams, and their estimated incidence of ventricular septal defects among premature infants was 4.5 per 1 000 live births in contrast to 0.95 per 1 000 for full term liveborn infants. They attributed this increased incidence to a general increase in congenital lesions in premature infants and to a more complete case ascertainment among small infants who routinely receive extensive evaluation and care. In the present study the methods are different, but again one finds an excess of ventricular septal defects among premature infants. A new hypothesis of the etiology of these findings is detailed

Materials and methods

Since 1959 the Collaborative Study on Cerebral Palsy and Mental Retardation has prospectively studied pregnant women at 13 collaborating institutions in order to evaluate the effects of perinatal events on the outcome of pregnancy By 1965 some 50 000 births had occurred to women enrolled in this study Among the study offspring who weighed more than 400 grams at birth 64 cases of isolated ventricular septal defects have been found (Products of conception weighing less than 400 grams have been defined as abortions.)

Ascertainment of abnormalities among the dead infants is not a problem since the autopsy rate is better than 90 per cent. Ascertainment among the living presents a number of difficulties hence the figures here presented are not to be construed as definitive incidence data. All of the 43 living infants have been examined by a pediatric cardiologist 8 have undergone catheter and or angiocardiographic studies The others have not required this adjunct to therapy Thus, although in all cases there was a definitive cardiologic diagnosis consideration has not been restricted to those in which the lesions were severe The 43 living patients reflect the complete clinical spectrum of isolated ventricular septal defects from spontaneous closure and maladie de Roger to pulmonary hypertension and

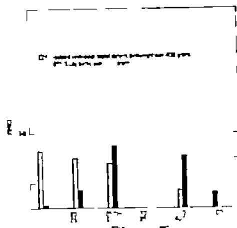


Fig 1 Frequency distribution of birth weights. See text.

cardiac failure due to a large left to-right shunt. Forty two per cent of the 64 patients with ventricular septal defects are Negro 47 per cent of the entire study population are Negro

Birth weights were known for 60 of the 64 infants with isolated ventricular septal defects. The average weight for infants with ventricular septal defects was 2,590 ± 77 grams, whereas the average birth weight for the core group of infants was 3 170 ± 4 grams. The frequency distribution of these birth weights is shown in Fig 1 The infants with ventricular septal defects were also gestationally younger than the core group Their average gestational age was 37 ± 0.7 weeks whereas the average gestational age of the core group was 39 ± 0 1 weeks. The frequency distribution of the gestational ages is given in Fig 2. The differences between the group with ventricular septal defects and the core group for birth weight and gestational age are both significant with $p < 0.001$ Fig 3 shows that infants with isolated ventricular septal defects are young and small not mature small infants whose intrauterine growth has been stunted The line drawn

*For these comparisons the t test has been used. This statistic tests the ratio of the difference between means to the standard error of that difference. The t test was used rather than the [illegible] test where variance [illegible] estimated since [illegible] preliminary assessment of variance within the different groupings, including the core group of more than 4,000 patients, showed the variance [illegible] be homogeneous.

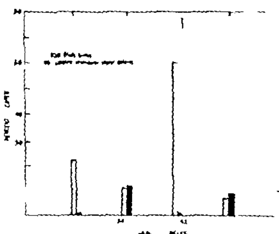


Fig. 2 Frequency distribution of gestational ages. See text.

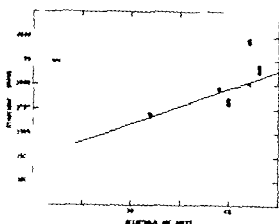


Fig. 3 Comparison of birth weight and gestational age in patients with isolated ventricular septal defects.

on this figure has the property of least squares with the formula

$$\bar{Y} = \bar{Y} + \frac{\Sigma XY - \Sigma X \Sigma Y/N}{\Sigma X^2 - (\Sigma X)^2/N}(X - \bar{X})$$

When the cases of ventricular septal defect are separated into deaths and survivors the following facts emerge. Table I shows all neonatal deaths of liveborn infants in 3 groups, those without heart disease (identified through October 1963), those with isolated ventricular septal defects, and those with all other types of cardiac defects. Because of the known relationship to birth weight, cases of twins and infants of diabetic mothers have been deleted from these and subsequent tables. Clearly the infants with cardiac defects other than ventricular septal defects are heavier than the infants with isolated ventricular septal defects or than those without cardiac abnormalities. The infants with ventricular septal defects are not significantly different in weight from those without heart disease who died in the neonatal period.

In Table II the group of living infants with ventricular septal defects are compared with the core group (essentially all of whom survived). Here it can be seen that the infants with ventricular septal defects are smaller than those of the core group. It does not appear to be the presence of associated malformations in the infants with ventricular septal defects which precipitates delivery or impairs growth since 30 per cent of the infants with isolated ventricular septal defects had extracardiac malformations whereas 43 per cent of the infants with other cardiac defects had associated abnormalities. Nor when allowance is made for birth weight do the patients with ventricular septal defects show an unusual predisposition to hyaline membrane disease.

It would appear therefore as though prematurity had revealed rather than caused or been caused by the defect. The data suggest that, had these infants gone to term many would not have presented with this defect. Clearly this can happen only if the ventricular septum continues to develop and close throughout pregnancy. Hoffman's data suggest also that it continues to close throughout the first year of life.

Discussion

The hypothesis is proposed that the normal time of ventricular septal closure may not be limited to the fourth and fifth postconceptive weeks but rather may extend for a minority of patients, throughout pregnancy and into the postpartum period. Such a hypothesis would explain the excess number of isolated ventricular septal defects among premature infants, and the lack of any abnormal autopsy findings in patients with spontaneously closed ventricular septal defects. It would also

Table I. Neonatal deaths in liveborn infants

Birth weight (Gm.)	Infants without congenital heart defects		Infants with isolated ventricular septal defects		Infants with all other congenital heart defects	
	Number	Per cent	Number	Per cent	Number	Per cent
500–2,500	378	70	7	87	19	36
> 2,500	163	30	1	13	34	64
	541	100	8	100	53	100

χ^2 = 26.81
= < 0.005.

Table II. Comparison of birth weights in living infants

Birth weight (Gm.)	Core group		Group with isolated VSD	
	Cases	Per cent	Cases	Per cent
2,001-2,500	1,418	8	7	21
2,501-3,000	4,654	25	9	26
3,001-3,500	7,521	40	15	44
> 3,501	5,060	27	3	9
	18,653	100	34	100

*Core Group—First Study pregnancy, single births.
χ^2 = 1.34.
p = < 0.025.

explain the disproportionate lack of ventricular septal defects among the autopsied adult population as compared to the living pediatric clinic population.[13]

This concept of continued growth of normal structure within the heart is not without precedent. For example, at birth the septum primum, which by the XVII horizon (approximately 35 days after conception) has appeared, developed, degenerated, and grown into essentially the natal relationship with the septum secundum, still has not fused with this secondary septum. Only by postnatal proliferation of the subendothelial connective tissue by some 600 to 700 per cent does the foramen ovale become obliterated sometime after the third month and usually before the end of childhood.[14] Since lack of closure is not usually a functional handicap, the exact time of closure has received scant attention. Similarly, through intimal proliferation, the ductus arteriosus becomes anatomically sealed sometime between the second and eighth postnatal weeks. Normally, the earliest phases of this process are recognizable during the third trimester and are accelerated after birth.[15] Striking changes also occur after birth in the histologic appearance of the sinoatrial and atrioventricular nodes, although these are readily identifiable from the sixth intrauterine week onward.[4]

Clearly then, the heart is far from structurally complete at birth. There is, of course, no precedent for organogenesis per se beyond the first part of the first trimester. But that is not what is proposed

What is proposed is that although the right and left bulbar ridges, the endocardial cushions and the muscular portions of the ventricular septum appear and develop during the fourth to the sixth intrauterine weeks their growth may not be limited to this period but may continue throughout pregnancy and into the first few years of life

Data are lacking on the precise location of ventricular septal defects which subsequently close spontaneously With this information at hand it would be possible to determine whether in fact closure is effected by hypertrophy of muscle bundles by scarring or by normal growth of tissue

The implications of normal closure throughout pregnancy and the postpartum period are many Teratogenesis need not be limited to the first trimester Studies of incidence and inheritance cannot ignore the implications of birth weight. Case ascertainment throughout infancy becomes essential and the importance of pathology to etiology is underscored

Summary

From the Prospective Collaborative Study on Cerebral Palsy and Mental Retardation 64 cases of isolated ventricular septal defects have been identified In these there has been a significantly lower mean birth weight and gestational age than in infants without heart disease as well as in those with cardiac defects other than ventricular septal defects The hypothesis is proposed that this is due to an essentially normal phenomenon whereby the right and left bulbar ridges and the endocardial cushions apparent in the heart since horizon XVI continue to grow throughout pregnancy and the postpartum period effecting closure either during the second or third trimester or the first few years of life The rationale for and consequences of this hypothesis are discussed

We gratefully acknowledge the assistance of Dr Max Halperi and Dr Maureen Henderson in the analyses of these data

REFERENCES

1 Streeter G L: Contribution to embryology No. 211 Developmental horizons in human embryos, age groups XI to XXIII Washington, D C 1948, Carnegie Institution of Washington, pp 144 and 170
2 Hamilton, W J Boyd, J D and Mossman, H W Absorption of the sinus venosus int the right atrium in Hamilton W J editor Human embryology Baltimore, 1962, Williams & Wilkins Company pp. 172 nd 174
3 Edwards J E Malformations of the ventricular septal complex, in Gould S E., editor Pathology of the heart, Springfield, Ill 1960, Charles C Thomas, p 316
4. Morris, E. W T Embryology of some congenital cardia anomalies, Thorax 20 158, 1965
5 Keith J D Rowe R D and Vlad, I Heart disease fancy nd childhood, New York, 1958 The Macmillan Company Embryology of congen tal heart disease (p 127) nd ventricular septal defect (p. 216)
6 Streeter G L Contributions to embryology N 197 Developmental Horizons in H nan Embryos, Age Groups XI to XXIII Washington, D C 1942 Carnegie Institution of Washington, p. 217
7 Evans, J R Row R D and Keith, J D Spontaneous closure of entricular septal defects, Circulation 22 1044 1960
8. Wade, G and Wright, J P Spontaneous closure of ventricular septal defects, The Lancet 1 737 1963
9 M jka, M Ry J and Bond D C Spontaneous repair of ventricular septal defect, Canad. M A J 82:317 1960.
10 Miller W I and Kovachevich R. Self-sealing ventricular septal defects of the heart. Am. Heart J 66 798, 1963
11 Hoffman, J I E and Rudolph A. M The natural history of entricular septal defects in infancy Am J Cardiol. 16:634 1965
12. Griffiths, S. P Bl menthal, S. Jameson, A. G., Ellis, K Morgan, B C nd Malm, J R. Ventricular septal defect, Am. J Med. 37:23, 1964.
13. P tten, B. M: The development of the heart Gould,[3] pp. 82-89

Coronary blood flow, energetics, and myocardial metabolism in idiopathic mural endomyocardiopathy (14 patients)

A. J. Brink, M.D.
C. M. Lewis, M.B., Ch.B.
Bellville, South Africa

This investigation presents the findings of a study of coronary blood flow and myocardial metabolism in patients who were believed to have idiopathic mural endomyocardial disease (IMED), the name given to idiopathic myocardiopathy seen in South Africa.[1]

This condition is the most common form of heart disease in the African.[2] It is not infrequent in the Cape Coloured and is seen in white subjects.[1] Little is known about the etiology and no studies have so far been made on the myocardial performance and metabolism.

It is recognized that this condition is different from endomyocardial fibrosis (EMF) as described from East, Central, and West Africa.

In South Africa, too, Löffler's fibroplastic endocarditis with eosinophilia occurs not infrequently[7] and may present with a clinical picture similar to that in IMED.

Thiamine deficiency with beriberi heart disease is an entity here and may similarly give rise to clinical confusion.

The possibility of an alcohol-induced cardiomyopathy must also be borne in mind in the clinical assessment of such cases.

It is of some importance, therefore, to have further information on the disturbance of myocardial function in idiopathic cardiomyopathy in order to understand better its nature and to help differentiate it both from the other forms of myocardial disturbances seen in this country and from the idiopathic cardiomyopathy which has been described from elsewhere.[8-10]

Studies on coronary blood flow and myocardial metabolism have been reported in idiopathic cardiomyopathy and in alcoholic cardiomyopathy by Wendt and associates and also in progressive muscular dystrophy[11] and in hypertrophic obstructive cardiomyopathy. Our findings will be compared with the findings in these cardiomyopathies and also with the findings described in valvular, hypertensive, and atherosclerotic heart disease.

Clinical material

Fifteen studies were carried out on 14 patients; 1 patient was studied twice with the lapse of a year. Although the patients

From the Department of Internal Medicine and the Degenerative Diseases Group of the Council for Scientific and Industrial Research, University of Stellenbosch Medical School, Karl Bremer Hospital, Bellville, Cape Province, South Africa.

This work was supported in part by the South African Atomic Energy Board.
Received for publication May 21, 1966.

*Professor of Internal Medicine. Address: P.O. Box 33, Bellville, Cape Province, South Africa.
**Research Associate, C.S.I.R.

were in the postabsorptive state the early morning meal which they had had may have preceded actual sampling of blood by as much as 3 hours In 6 patients the observations were made before and after exercise All patients had cardiomegaly and all except 2 had evidence of past or present congestive cardiac failure Hypertensive valvular or atherosclerotic heart disease was excluded No systemic illness which could involve the heart could be found The thiamine status of 12 patients was determined by means of the transketolase method of Wolfe and associates[10] and Brin and associates[11] Serum tests for syphilis were available and were negative in 11 patients.

Four patients subsequently died and in 3 patients an autopsy diagnosis of idiopathic mural endocardial disease as described by Becker[1] was established

The patients ranged in age from 4½ to 55 years (7 were in the age-group of 30-45 years) There were 11 males and 4 females and all were non white there were 9 African (Bantu) and 7 Cape Coloured patients.

A protodiastolic gallop rhythm was commonly present and a murmur of mitral incompetence could be heard in the majority of patients. Evidence of pulmonary emboli was fairly frequent

A *summary of the pertinent details* is set out in Table I

Methods

Cardiac catheterization procedures These consisted of right and retrograde left heart

Table I Clinical data thiamine status serology and autopsy findings in 14 patients with

Patient	*Race Sex*	*Age (yr)*	*Cardiac failure*		*B.P. (mm Hg)*	*Gallop rhythm*
			Previous	*Current*		
1 (K.V.)	Cape Coloured, female	51	+	−	110/70	+
		52	+	+		+
2 (P.V.)	Cape Coloured, male	43	+	+	105/90	+
3 (M.K.)	Cape Coloured, male	4½	−	−	70/40	+
4 (J.R.)	Cape Coloured male	12	+	+	100/80	+
5 (M.P.)	Cape Coloured, female	5	−	−	145/80	−
6 (J.J.)	Bantu male	43	+	−	120/80	+
7 (S.M.)	Bantu, male	40	+	*	105/65	−
8 (A.L.)	Cape Coloured male	43	+	−	140/90	+
9 (M.T.)	Cape Coloured female	55	+	+	140/100	−
10 (J.M.)	Bantu, male	42	+	+	140/90	+
11 (F.E.)	Cape Coloured male	26	*	−	100/60	−
12 (C.N.)	Bantu male	38	*	−	140/80	+
13 (S.N.)	Bantu male	38	+	+	105/70	+
14 (A.Z.)	Bantu male	46	+	−	140/85	+

*Data not available.

catheterization and intubation of the coronary sinus. Samples of blood for biochemical analyses were obtained from the arterial side via a catheter in the brachial artery or aorta and from the coronary sinus via the indwelling catheter. Pressures were recorded by means of a Statham P23D strain gauge and a direct writing Sanborn polygraph. Cardiac output was determined by the Fick principle. Oxygen volumes were determined by the method of Van Slyke and Neill.[22]

In 2 patients, myocardial blood flow was determined by selective injection of xenon 133 into the ostia of the right and left coronary arteries, using a Sones type of coronary artery catheter.[23] In 11 other patients, myocardial blood flow was determined by the nitrous-oxide method[24] before and after exercise. Exercise consisted of a pedaling motion of the legs which were supported by an assistant for 6 minutes at the end of a 15-minute period of inhalation of nitrous oxide. The actual measurement of the coronary flow was begun at the end of 3 minutes of exercise and the specimens of coronary sinus and arterial blood for the determination of metabolism were taken between the collection of the third and fourth (last) specimens of blood for the determination of coronary flow.

Left ventricular work and efficiency were calculated according to the formulae proposed by Bing and associates.[24] The tension-time index (TTI) per *minute* in millimeters of mercury per second was obtained by planimetric integration of the area under the systolic portion of the aortic

idiopathic myocardiopathy

Systolic murmur	*Pulmonary embolism*	*Syphilis serology*	*Thiamine deficiency*	*Digitalis*	*Autopsy findings*
+	+	−		+	Not performed
+	+			+	
+	−	−	−	+	Mural endomyocardiopathy
+	−	−		−	
+	+	−	−	+	Mural endomyocardiopathy
+	−	−		−	
+	−	−	−	+	
+	−	−	−	+	
+	+	−	−	+	
−	−	−		+	Mural endomyocardiopathy
+	+	−	−	+	
−	−	−	−	+	
−	−		−	−	
+	−		−	+	
−	−	−	−	+	

pressure curve and is equal to the product of mean systolic pressure and the duration of systole.[illegible] The product of heart rate and TTI was expressed as pressure time per minute (PTM). Internal myocardial efficiency was calculated from the ratio of PTM to myocardial oxygen consumption.[illegible] The oxygen utilization coefficient[illegible] was determined as the quotient of minute oxygen consumption divided by the product of the systolic duration (in seconds per minute) and units of pressure work (kilogram meters) performed.

Myocardial consumption of oxygen and of other substrates was calculated as the product of coronary arteriovenous difference of the substance and the coronary blood flow. The nitrous-oxide technique measures that fraction of myocardial blood flow which is drained through the coronary sinus. The latter is estimated to be 85 per cent of total coronary blood flow.[27] In our laboratory we have established a close correlation between coronary blood flow as determined by the nitrous-oxide method and that calculated by taking 85 per cent of the combined right and left coronary arterial flows obtained by selective injection of xenon 133 into the coronary ostia.[illegible]

We have used this latter method to assess myocardial consumption of oxygen and other substrates from the arteriovenous differences in the 2 patients in whom xenon 133 was used for determining coronary blood flow.

Biochemical methods. Blood glucose was assayed by the glucose-oxidase method.[illegible] The lactate content was determined by the enzymatic method (UV method with DPN)[illegible] as modified by Opie and associates.[illegible] The determination of pyruvate was by the UV method with DPNH.[illegible] Concentrations of free fatty acid (unesterified fatty acids, nonesterified fatty acids) in the plasma were determined by the method of Dole and Meinertz.[illegible] Creatine phosphokinase and aldolase values of the blood were determined by the UV method with DPNH using Biochemica Boehringer kits.

Inorganic phosphate was determined according to the method of Hiller.[illegible]

The usual statistical methods, as applied to small numbers, were used. Before- and after-exercise results were tested for significance by the method of paired sample analysis.

Results

A. Studies at rest (15). The results are contained in Tables II and III.

CORONARY BLOOD FLOW (CBF). The mean CBF of 67.4 ml. per minute per 100 grams of heart muscle is of the same order as the mean normal values reported by other groups of workers whose findings have been summarized by Rowe[illegible] and Gorlin.[illegible] When compared with the values reported in 10 normal subjects by Wendt and associates,[1] the difference is not significant.

METABOLISM. The substrate balance was positive for glucose in all except 2 patients, for pyruvate in 7 patients, and for lactate in all except 4 patients. The mean values obtained for pyruvates and lactates do not differ significantly from the values in normal subjects studied by Wendt and associates.

Free fatty acids had a positive balance in all patients. The arterial levels were not significantly affected by the infusion of heparinized fluid during the catheterization procedure. Heparinization has been shown[27] to cause a difference in the levels of free fatty acids.

Oxygen extraction and consumption had a mean value not significantly different from that of normal subjects.

Redox potential gradient[4] across heart muscle was positive in 10 patients, nil in 1 patient, and negative in 4 patients. The mean of + 6.6 mv. is not significantly different from the mean of +2.3 mv. of Wendt and associates.

Inorganic phosphorus in coronary sinus blood was above mean normal values, 4.66 mg. per 100 ml. Five patients had values greater than 5.5 mg. per 100 ml. Only 1 of these 5 patients, however, had a negative redox potential gradient.

The cytoplasmic enzyme aldolase and the mitochondrial enzyme creatine phosphokinase had negative mean myocardial balances, which suggests efflux of these enzymes into coronary sinus blood.

*Chemicals: The chemicals and enzymes for the determination of glucose, lactate, and pyruvate as well as of aldolase and creatine phosphokinase, are obtained from Boehringer and Soehne GmbH, Mannheim, Germany. Perchloric acid (60 per cent Analar) was obtained from British Drug Houses, Ltd., Poole, England.

DYNAMICS The cardiac index of 2.9 L. per minute per square meter was below reported normal mean values.[1,2] The difference approached statistical significance ($p > 0.05 < 0.1$) Left ventricular efficiency per cent of 24.25 is similar to the normal mean values of Bing and associates.[31]

The tension time index (mm. Hg-sec./min.) or PTM (pressure time-per minute)[33] is *less than reported normal*.[34]

The mean value for internal efficiency ratio of 384.7 was above the normal. The oxygen utilization coefficient had a mean value of 0.072, which is close to the mean normal of 0.076.[34]

It is of interest that 3 of the patients who died (P. V., J. R., and M. T.) all had exceedingly low values for mechanical efficiency ratios and PTM and above average normal values for oxygen utilization coefficient. These parameters were not available in the fourth patient who died (K. V.).

Mean coronary vascular resistance (dynes. sec./cm.^{5} $\times$ 10^{3}) had an elevated mean value of 98.17 (normal mean 69.4 dynes.-sec./cm. $\times$ 10^{3}).[33] Again all of the patients who died and in whom this parameter was determined had values well below normal.

B. Studies with exercise (6). Exercise in our patients was moderate. It was extended over a 6-minute period following the observations of Donald and associates[35] that the maximal level of lactic acidemia occurs between the fifth and tenth minutes of exercise both for normal and cardiac subjects and that a relatively steady state in arterial blood levels is then obtained. There is, however according to these authors, a greater increase in lactic acid in the arterial blood of cardiac patients.

CORONARY BLOOD FLOW. The coronary blood flow increased in all but 1 patient, the mean increase was 35 per cent over the resting value, this being more than the mean increase of 25 per cent in normal subjects reported by Gorlin.[36] Nevertheless the change was *found to be not significant*.

METABOLISM. Oxygen extraction values showed no change, having a mean of 10.5 volumes per cent before exercise and 10.7 volumes per cent after exercise.

Oxygen consumption changed from a mean of 7.11 ml. to 9.91 ml. Again, significance could not be proved.

The arterial level of all carbohydrate substrates (*glucose, pyruvate and lactate*) was elevated significantly. Among myocardial balances and usage only those for pyruvate were significantly altered, however. Coronary sinus blood lactate was significantly elevated but lactate usage was not changed significantly from a mean of 2.11 to 3.73 mg.

Total carbohydrate contribution to aerobic metabolic demands was reflected in an increase in the oxygen extraction ratio from a mean of 48.1 to 120.1 per cent. The contribution by free fatty acids changed from 51.5 to 74.9 per cent. In neither case could the change be shown to have statistical significance.

Levels of inorganic phosphorus and concentrations of enzymes were not determined in coronary sinus blood after exercise.

DYNAMICS Only PTM (mm. Hg sec./min.) and the internal efficiency ratio could be calculated after exercise. The former increased from 2,517 to 3,020 and the latter became reduced from mean 437 to 328. Neither change had statistical significance.

Discussion

Idiopathic mural endomyocardiopathy is known to occur in children.[11] Our series included 3 children. It has been well documented in adults both clinically and pathologically.[3,4,11-13]

Our patients illustrate the salient features of a subacute or chronic disorder of heart muscle associated with the findings of a gallop rhythm and a murmur of functional mitral incompetence. Other possible causes for the cardiac condition were considered but there was no substantiating evidence for these. Autopsy evidence of the diagnosis was forthcoming in 3 patients. This series of patients may thus be accepted as having the South African type of idiopathic endomyocardiopathy.

During rest the coronary blood flow was found to be within the normal range. Oxygen extraction and usage were normal. With exercise the coronary blood flow increased in 5 of 6 patients studied, the mean increase being more than the reported increase for normal patients and approaching a significant level of change.

Exercise did not increase the oxygen

Table II Metabolic studies at rest and during exercise in 14 patients with idiopathic myocardiopathy

		Coronary blood flow (ml./min./100 Gm. LV)	Oxygen extraction (Vol. %)	Arterial blood levels and myocardial arteriovenous differences: Arterial glucose (mg./100 ml.)	Glucose balance (mg./100 ml.)	Arterial pyruvate (mg./100 ml.)	Pyruvate balance (mg./100 ml.)	Arterial lactate (mg./100 ml.)	Coronary vein lactate (mg./100 ml.)	Lactate balance (mg./100 ml.)	Arterial free fatty acid (mEq/100 ml.) (before heparin)	Arterial free fatty acid (mEq/100 ml.) (after heparin)	Free fatty acid balance (mEq/100 ml.) (before heparin)	Free fatty acid balance (mEq/100 ml.) (after heparin)
Patients	Mean S.E.	67.4 ±9.65	11.1 ±0.506	71.70 ±3.70	5.91 ±1.37	0.86 ±0.09	0.065 ±0.057	8.51 ±1.05	4.535 ±0.951	1.02 ±0.53	0.0930 ±0.0166	0.0654 ±0.0112	0.0142 ±0.0029	0.0115 ±0.0037
Normal subjects (Wendt et al., 1962)	Mean S.E.	87.0 ±8.75	10.5 ±0.39			0.52 ±0.067	0.18 ±0.049	6.27 ±0.38		1.83 ±0.35				
	p	0.3	0.4			0.03	0.4	0.7		0.9				
Before exercise	Mean S.E.	70.07 ±17.93	10.5 ±1.05	70.23 ±3.25	6.01 ±1.67	0.81 ±0.16	−0.007 ±0.077	6.01 ±1.76	4.16 ±1.026	1.65 ±0.96	— —	0.0541 ±0.0096	— —	0.0078 ±0.0015
During exercise	Mean S.E.	91.03 ±13.07	10.7 ±1.08	83.33 ±3.37	11.29 ±5.27	1.31 ±0.19	0.325 ±0.096	12.64 ±1.97	9.176 ±1.203	3.48 ±1.17	— —	0.0771 ±0.0207	— —	0.0151 ±0.0059
	p	0.3	0.8	0.05	0.7	0.05	0.01	0.05	0.02	0.7		0.8		0.9

Table II Cont'd — Metabolic studies at rest and during exercise in 14 patients with idiopathic myocardiopathy

		Myocardial usage (per 100 Gm. per minute)						Oxygen extraction ratio (%)						Redox potentials of enzyme activity							
		Oxygen (ml.)	Glucose (mg.)	Pyruvate (mg.)	Lactate (mg.)	Free fatty acid (mEq.) (before heparin)	Free fatty acid (mEq.) (after heparin)	Glucose	Pyruvate	Lactate	Total carbohydrate	Free fatty acid (before heparin)	Free fatty acid (after heparin)	Arterial (mv.)	Coronary sinus	Gradient (ΔEh)	Arterial aldolase (milliunits/ml.)	A-V difference (milliunits/ml.)	Arterial C.P.K. (I units/ml.)	A-V difference (I units/ml.)	Inorganic phosphorus (mg./100 ml.)
Patients	Mean	7.34	3.903	0.076	1.567	0.0073	0.0091	40.4	0.29	11.0	49.9	76.6	66.5	−264.6	−247.9	+6.6	2.36	−0.66	0.06	−0.24	4.06
	S.E.	±0.96	±1.248	±0.064	±0.830	±0.0021	±0.0037	±9.3	±0.53	±4.14	±8.53	±15.3	±20.3	±4.1	±6.3	±3.4	±0.47	±0.87	±0.25	±0.44	±0.42
Normal subjects (Wendt et al. 1962)	Mean	8.50														2.33					
	S.E.	±0.44														±1.04					
	p	0.4														0.4					
Before exercise	Mean	7.11	9.311	0.019	2.110	—	0.0061	41.3	0.007	14.0	45.1	—	61.6	−255.6	−43.5	±12.0					—
	S.E.	±1.72	±1.037	±0.062	±1.623	—	±0.0009	±13.6	±0.498	±7.61	±14.06	—	±16.4	±4.3	±7.6	±4.5					—
During exercise	Mean	9.91	11.706	0.114	3.730	—	0.0124	91.2	2.26	26.6	150.1	—	74.0	−263.6	−251.5	+–3					—
	S.E.	±4.81	±6.25	±0.169	±1.314	—	±0.0023	±50.9	±0.71	±10.1	±67.01	—	±22.3	±3.6	±3.4	±2.6					—
	p	0.5	0.3	0.05	0.5		0.3	0.9	0.01	0.3	0.3		0.9	0.3	0.3	0.1					

Table III Resting and exercise myocardial energetics in 14 patients with idiopathic myocardiopathy

		Cardiac index (L/min/M²)	Left ventricular pressure work (Kg M/min)	PTM = TTI/min (mm Hg sec/min)	Coronary diastolic vascular resistance (dynes-sec/cm⁵ × 10³)	Mechanical efficiency ratio per cent (per 100 Gm LV)	Internal efficiency ratio (PTM/QO)	Oxygen utilization coefficient (ml O₂/100 Gm./systolic sec./Kg M)
Patients	Mean	2 92	4 09	2 193	98 175	24	384 7	0 072
	S.E.	±0 35	±0 69	±178 2	±16 155	±5 1	±48 0	±0 019
Normal subjects (Wendt et al 1962)	Mean	3 80						
	S E	±0 25						
	p	0 1						
Before exercise	Mean			2 517			437 0	
	S E			±326 1			±71 6	
During exercise	Mean			3 020			328 2	
	S E			±426 8			±52 2	
	p			0 05			0 1	

extraction which had been found to be normal at rest.

Studies on coronary blood flow in idiopathic cardiopathy by Wendt and associates in hypertensive valvular and atherosclerotic heart disease[17] and in mitral stenosis by Frank and associates and in severe aortic stenosis by Rowe and associates[1] show normal resting values of coronary blood flow with an increase in exercise but also a definite increase in arteriovenous oxygen differences.

Substrate metabolism of carbohydrates and fats appears to be normal at rest with fats in the form of free fatty acids making the larger contribution to energy requirements. This follows the normal pattern as described by Bing[14] and Ballard and associates.[17]

Like the patients with idiopathic myocardiopathy described by Wendt and associates some patients showed a negative extraction of glucose pyruvate and lactate

The metabolic pathways appeared to be oxidative and at rest there is no indication of anaerobic metabolism The lactate pyruvate redox potential gradient across the heart muscle was consistently positive a point against anaerobic metabolism

Although the levels of inorganic phosphorus were elevated in coronary sinus blood the absence of a negative redox potential was against an uncoupling of oxidative phosphorylation as described by Sundermeyer and associates[14] for the heart condition in muscular dystrophy

On exercise the supply of energy tended to come more from carbohydrate sources, again in keeping with normal expectations. The arterial levels of glucose pyruvate and lactate were all significantly elevated. Only pyruvate usage and extraction were significantly increased however The increased coronary sinus lactate and the shift of redox potential to a less positive value (from a mean of + 12 to a mean of + 3) indicated a tendency toward anaerobic metabolism In 2 patients the redox potential actually changed to negative values. One of these 2 patients (C V) showed negative extraction and usage of glucose and lactate and a reduced oxygen extraction ratio fo free fatty acids. In this pa

tient, anaerobic metabolism appears to be fairly certain.

The negative balance of the enzymes aldolase and creatine phosphokinase suggests an increased cell permeability for these enzymes, but cannot be explained on the basis of anoxia as has been shown to occur experimentally [44-46]

Despite the apparent normal coronary blood flow and metabolism at rest, myocardial performance is below normal. This is evidenced by the low cardiac index, the reduced PTM and the reduced left ventricular work.

The relationship of work to oxygen usage as expressed in the left ventricular mechanical efficiency ratio the internal efficiency ratio and the oxygen utilization coefficient was, however in the normal range

It was noteworthy that in the 3 patients who died relatively soon after these investigations (P. V. J. R. and M. T.) the myocardial performance (measured as left ventricular work and PTM) was abnormally low and the efficiency indices were much reduced. The oxygen utilization coefficient was increased. In all instances the indications were that less mechanical work was being performed at greater oxygen cost. This late finding appears to carry a grave prognosis.

In these same patients the coronary vascular resistance was reduced in contrast to the elevated values in the other patients, another finding which *seems therefore to* be associated with a poor prognosis.

Conclusions

1 The metabolic pattern in idiopathic mural endomyocardiopathy is similar to that described for idiopathic cardiomyopathy and alcoholic cardiomyopathy. The main difference however is that the oxygen extraction by heart muscle is not increased either at rest or during exercise. This is also in contrast with the findings of studies in hypertensive and valvular heart disease.

2 At rest, coronary blood flow is normal and substrate metabolism is normal and oxidative. There is no evidence for the occurrence of anerobic metabolism.

3 The present work does not suggest an uncoupling of oxidative phosphorylation to explain the metabolic upset as it appears to do in the heart condition associated with the muscular dystrophies.

4. Exercise tends to produce anaerobic mechanisms of energy supply

5 The myocardial performance is reduced although the efficiency ratios remain normal until late in the course of the disease. When they are reduced the prognosis appears to be grave.

REFERENCES

1. Becker B. J. P. Idiopathic mural endocardial disease in South Africa, Med. Proc. 9 124 1963
2. Schwartz, M. B. *Schamroth L., and Seftel, H. C.* The pattern of heart disease in urbanised (Johannesburg) Africans, Med. Proc. 4:275 1958.
3. Cosnett, J. E. Heart disease in the Zulu, especially cardiomyopathy in cardiac infarction Brit. Heart J. 21 76, 1962.
4. Weber H. W. Parietale endomyokarditis in die Karl Bremer-hospitaal, South African M. J. 37 148, 1963.
5. Report of joint seminar of the Departments of Pathology and Medicine of the University of the Witwatersrand. Some African cardiopathies, South African M. J. 31:854 1957
6. Brink, A. J. and Weber H. W. Endomyocardial fibrosis (E.M.F.) of East, Central and West Africa compared with South African endomyocardiopathies, South African M. J. 40 455 1966.
7. Brink, A. J. and Weber H. W. Fibroplastic parietal endocarditis with eosinophilia. Loffler endocarditis, Am. J. Med. 34:52, 1963.
8. Schrire, V. and Gant, J. The electrocardiographic changes associated with beriberi heart disease. South African J. Lab. & Clin. Med. 5 195 1959
9. Brink, A. J. Lochner A., and Lewis, C. M. Thiamine deficiency and beriberi heart disease Biochemical and clinical investigations, South African M. J. 40:581 1966
10. Sanders, V. Idiopathic disease of myocardium Arch. Int. Med. 112 76, 1963
11. Stuart, K. L. and Hayes, J. A. A cardiac disorder of unknown aetiology in Jamaica, Quart J. Med. 32:99 1962.
12. Andrade Z. A. and Guimarães, A. C. Endomyocardial fibrosis in Bahia, Brazil Brit. Heart J. 26:813 1964
13. Coelho, E. and Pimentel, J. C. Diffuse endomyocardial fibrosis, Am. J. Med. 35:569 1963
14. Wendt, V. E. Stock, T. B. Hayden R. O. Bruce T. A., Gudbjarnason, S. and Bing R. J. The haemodynamics and cardiac metabolism in cardiomyopathies, M. Clin. North America 46 1445 1962.
15. Sunderméyer J. F. Gudbjarnason, S. Wendt V. E., Den Bakker P. B. and Bing R. J. Myocardial metabolism in progressive muscular dystrophy Circulation 24 1348 1961
16. Gorlin, R., Cohen, L. S. Elliott, W. C., Klein, M. D. and Lane F. J. Haemodynamics of

muscular subaortic stenosis (obstructive cardiomyopathy), in *Ciba Foundation Symposium* Cardiomyopathies edited by Wolstenholme and O'Connor London, 1964 J & A Churchill, Ltd.

17. Messer J V and Neill W A Oxygen supply of the human heart Am J Cardiol 9 384 1962

18. Rowe G G Alfonso S Lugo, J E Castillo, C A Boake W C and Crumpton, C W Coronary blood flow and myocardial oxidative metabolism at rest and during exercise in subjects with severe aortic valve disease Circulation 32:251 1965

19. Frank M J Levinson G E and Hellems, H K. Left ventricular oxygen consumption, blood flow and performance in mitral stenosis Circulation 31:824 1965

20. Wolf S J Brin M and Davidson C S. The effect of thiamine deficiency on human erythrocyte metabolism, J Clin I vest. 37 1476, 1958

21. Brin, M Tai, M Ostashever A S and Katinsky H. The effect of thiamine deficiency on the activity of erythrocyte hemolysate transketolase Ann New York Acad Sc 98:528 1962.

22. V Slyke D D and Neill, J M The determination of gases in blood and other solutions by vacuum extraction and manometric measurement J Biol Chem 61:523 1924

23. Ross R S Ueda, K Lichtlen P R and Rees J R Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries Circulation Res. 15:28 1964

24. *Bing, R J Hammond M M Handelsman, J C* Powers, S. R Spencer F C Eckenhoff J E. Goodale W T Hafkenschiel, J H and Kety S S The measurement of coronary blood flow oxygen consumption and efficiency of the left ventricle in man AM HEART J 38 1 1949

25. Sarnoff S J Braunwald, E. Welch, G H J Case R B Stainsby W N and Macruz R. *Hemodynamic determinants of oxygen* consumption of the heart, with special reference to the tension-time index, Am J Physiol. 192 148 1958

26. Gorlin R. Brachfeld, N MacLeod, C. and Bopp P Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work, Circulation 19 705 1959

27. Gensini, G. G *Di* Georgi, S Coskun O Palacio, A., and Kelly A E Anatomy of the coronary circulation in living man. Coronary venography Circulation 31 778, 1965

28. Brink, A. J Lewis, C. M and Van Heerden P D R. Coronary blood flow (by two methods) in relation to myocardial performance and oxygen utilization in cardiomyopathies I preparation.

29. Huggett, A. St. G and Nixon, D A. Enzymatic determination of blood glucose Biochem. J 66 12P 1957

30. Horn, H. D and Bruns, F H Quantitative Bestimmung von L(+)-milchsäure mit milchsäuredehydrogenase, Biochim et Biophys. Acta 21:378, 1956.

31. Opie, L. H Shipp, J C., Evans, J R., and Leboeuf B. Metabolism of glucose-U-C^{14} in perfused rat heart, Am. J Physiol. 203:839 1962.

32. Redetzki, H Bloedorn, H and Banal, H W Einfluss der Thioctinsäure auf den Brenztraubensäure und α-ketoglutarsäure-Blutspiegel bei Leberkranken, Klin. Wchnschr 34:845 1956.

33. Dole V P and Meinertz, H Microdetermination of long-chain fatty acids in plasma and tissues, J Biol. Chem. 235:2595 1960

34. Hiller A Practical clinical chemistry ed. 2, Springfield, Ill, 1957 Charles C Thomas, p 118

35. Rowe, G G The regulation of coronary blood flow in man in normal and abnormal conditions, M Clin. North America 46 1421 1962.

36. Gorlin, R. Measurement of coronary blood flow in health and disease, Jones, A. M editors Modern trends in cardiology London, 1960, Butterworth & Co Ltd., p 191

37. Ballard, F B Danforth W H Naegle, S., and Bing, R. J Myocardial metabolism of fatty acids, J Clin. I vest. 39 717 1960

38. Gudbjarnason S. Hayden, R O Wendt, V F Stock, T B. and Bing, R J Oxidation reduction in heart muscle Theoretical and clinical considerations, Circulation 26:937 1962.

39. Donald, K. W Gloster J Harris, E. A Reeves, J and Harris P The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease, AM. HEART J 62:494 1961

40. Stein H Shaper M H., Wayburne, S., and Isaacson, C Cardiomyopathy in African children, Arch Dis. Childhood 39:610 1964.

41. Gillanders, A. D Nutritional heart disease, Brit. Heart J 13 177 1951

42. Becker B J I Chatgidakis, C B., and Van Lingen B. *Cardiovascular collagenosis with* parietal endocardial thrombosis A clinicopathologic study of forty cases, Circulation 7:345 1953

43. Keller K. J Chester E., Seftel, H C., and Walker A. R. P Tropical cardiomyopathy Lancet 2:525 1963.

44. Bing R J Siegel, A., Ungar J and Gilbert, M Metabolism of the human heart. II Studies on fat ketone and amino acid metabolism, Am J Med. 16:504 1954

45. Zierler K. L. Diffusion of aldolase from rat skeletal muscle A index of membrane permeability Am. J Physiol. 190:201 1957

46. Zierler K. L Increased muscle permeability to aldolase produced by depolarization and by metabolic inhibitors, Am. J Physiol. 193:534 1958.

47. Bing, R. J and Danforth, W Metabolic changes in heart muscle following anoxia, Am J Physiol. 197 1147 1959

Paradoxical precordial motion and wasted left ventricular work: The concept of cardiac dyssynergy

John O Langley M D
*Alvaro Martínez, M.D.***
*Ali Fakhro M D****
*Peter Dinvoisin M.D.****
T R Harrison M.D
Birmingham Ala

In young persons with normal hearts the largest precordial deflections with the cardiac cycle are those due to change in volume and thus are inward during systole and outward during diastole. As ejection begins, there is a brief outward recoil motion, largest at the apex. These several deflections as well as certain other small systolic outward movements, have been described in detail in previous studies.

The exaggerated abnormal systolic outward motions that occur in patients with ischemic heart disease[1-4] and in those with ventricular hypertrophy[4] have been discussed in other communications from this laboratory. That a certain amount of cardiac work is wasted (i.e. not directly utilized during isovolumic contraction for elevation of pressure or subsequently for ejection) in producing these paradoxical movements is obvious. The crucial question is How much. The studies on dogs by Tennant and Wiggers of Murray and Tyson and associates,[9] which have been summarized elsewhere[14] suggest that this wastage is of significant degree. The purpose of the present study is to attempt to answer the question in man.

Subjects and methods

The persons studied were the following

a Thirteen individuals with normal hearts, as judged by clinical and electrocardiographic criteria. Of these 10 were 39 years old or less and 3 were 40 years old or more.

b Fifteen patients with ischemic heart disease as indicated either by typical anginal pain or by myocardial infarction in the past, or by both. One of them had normal kinetocardiographic records whereas the others were selected because

From the Department of Medicine, Medical College of Alabama, Birmingham, Ala
This work was supported in part by Grants No [illegible] and [illegible] from the National Institutes of Health, and by the Elizabeth and Barbara Ingalls Fund, the Calhoun County Heart Association, and Mr Hugh Kaul.
Received for publication May 2, 1966
*Fellow of the Alabama Heart Association.
**Trainee of the National Heart Institute
***Trainee of the United States Public Health Service
****Fellow of the United States Public Health Service.
Address correspondence to Dr Harrison, Department of Medicine, Medical College of Alabama, Birmingham Ala., [illegible].

they exhibited varying degrees of paradox ical outward systolic motions (bulges) Multiple studies were made in of these subjects.

c Thirteen patients with lesions (6 aortic valvular ? hypertensive ? congeni tal) that place an increased load on the left ventricle Evidence of left ventricular hy pertrophy was seen in the ECG in 10 of these subjects, and in the kinetocardiogram (*paradoxical systolic motion in the region* of the apex) in 11 Nine of these patients underwent cardiac catheterization on the day before or after the studies of precordial motion

d Five subjects in whom the wasted work was measured during aortic cathe terization with simultaneous determina tion of aortic pressure and left ventricular stroke volume by the method of Jones and associates [1]

Patients with excessive loads on the right ventricle only were omitted from the study

The *apparatus employed* (Fig 1) con sists of a platform supported by four ad justable feet which can be fitted into the intercostal spaces overlying the area in the apical region which displayed the largest outward movement as determined by previous KCG s taken from the several intercostal spaces (fourth to sixth) in the V to V vertical lines. The response of the recording apparatus (a Sanborn 4-channel

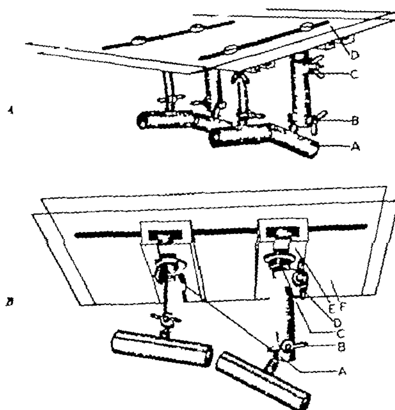


Fig *1* *Section A* View of precordial eight carriage from above. The apparatus is constructed of aluminum and consists of the following major parts *A* Adjustable foot designed t rest within the i tercostal space over lying the precordial "bulge *B* Adjustment ring ut by which "foot can be rotated to fit configuration of chest w ll, *C* Sleev hich allow extension of "foot to further facilitat adjustment t fit configuration of chest wall. *D* Platform top hich measured flat circular eights are sequentially placed *Section B* View of precordial eight carriage from below Only t of the four feet are show in order to oid confusion, *A* Wing nut which llow for adjustment of "foot position in horizontal plane. Differences in i terspace idth can thereby be compensated for *B* Same as *B* in Section A *C* Adjustment plus bolt, which llow same move ments of foot as *A* in Section *B* *D* Wing nut hich fixes sleev (*C* in Section A) in position *E*, Track in which feet are ttached to underside of platform (*F* in Section *B*), nd through hich feet can be moved in horizontal plane. *F* Underside of platform (*see D* in Section *A*).

direct writer) to movement of a known distance was measured immediately prior to the study of each subject, so that at any given dial setting the millimeters of deflection of the trace could be converted into actual millimeters of movement of the chest wall. The sensitivity of the recorder remained essentially constant during the period (about 3 years) of the study.

The procedure employed was as follows. The electrocardiogram (Leads I and II), the carotid pulse, and the movement of the platform were recorded simultaneously. The recumbent subject assumed a slightly oblique position with a pillow under the left axilla and shoulder. Weights were then added progressively to the platform until either (1) the weight × distance product became constant, decreased slightly, or showed little increase or (2) the procedure became so painful that the subject was unwilling to tolerate additional weight. The latter situation was occasionally encountered.

In the measurement of the records the level of the curve of platform movement at 0.04 second after the onset of the QRS was assumed to be the diastolic base line.[4] The height and duration of the outward motion of the platform above this level were determined. Since the weight on the platform was known, the work would then be calculated in gram meters. The integral of work in gram meter seconds was calculated by measuring the area under the curve with a planimeter. Typical findings for a normal person and for a patient with a moderately large bulge as progressively more weight was utilized are shown in Fig. 2.

Critique of method. The procedure is crude and indirect. It is uncomfortable for all subjects, painful for some, and intolerable for a few, especially those with small chests and narrow intercostal spaces.

We had assumed a priori that with added weight there would be a corresponding decline in excursion and that the product mass × distance would remain relatively constant. The observation that such a work plateau occurred only with the heavier weights (and not at all in a few subjects) was initially surprising. The explanation is probably as follows. Some of the intercostal tissues are relatively rigid and ordinarily much of the energy wasted by the heart in a systolic protrusion is presumably absorbed in stretching these structures. The motion that one feels (or records) therefore represents only the energy above and beyond such absorption. It is probable that one has to add enough weight to the chest to displace the relatively rigid intercostal membrane slightly toward the thoracic cavity before the major fraction of the cardiac work involved in the bulge begins to be reflected at the surface. Although proof of this explanation is lacking, the observation that the work × distance plateau occurs at approximately the same weight regardless of the cardiac status (Fig. 2) is evidence that some structure other than the heart is responsible for the delayed work plateau.

The configurations of the records in Fig. 2 are susceptible to multiple interpretations. Not only are there large early systolic upstrokes, indicating that the weight is being lifted, but during the mid and late portions of systole there are large downstrokes showing that the weight is descending. There can be no doubt that the early lift represents work done *on* the weight *by* the heart. Is not the converse also true and does not the subsequent systolic descent of the weight represent work done *on* the heart *by* the weight? If so, does not this represent an additional force favoring ejection and should not one, therefore, subtract the downstroke from the upstroke in measuring the wasted work? Since this question is fundamental to the evaluation of the significance of our data, it may be considered in some detail.

The systolic descent of the weight (Fig. 2) is obviously caused immediately by inward motion of the intercostal spaces. This could conceivably be due to several causes: (1) an actual indentation or compression of the left ventricular wall with displacement of blood, (2) a displacement of the entire heart away from the weight, (3) displacement of a portion of the left lung, (4) compression of the adjacent portion of the left lung with displacement of a small amount of air. Of the various substances (solids, liquids, and gases) and tissues (heart, blood, and lung) that might be displaced, those with the lowest specific gravity (air and lung) offer the least re-

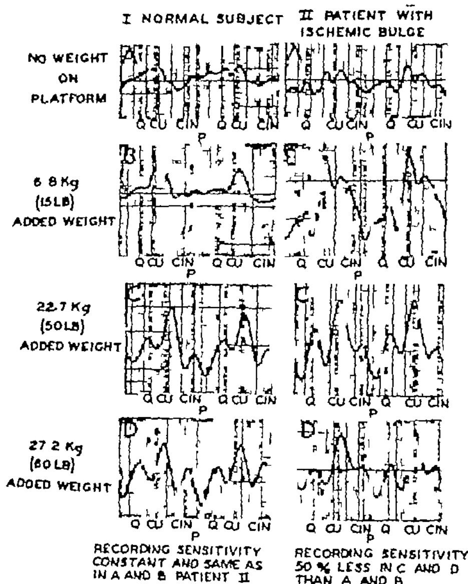


Fig. 1. Effect on precordial movements of progressive loading of precordial platform. Paper speed 50 mm. per second. Two complexes are shown beginning and ending with the P wave. The dotted lines *Q*, *CU*, and *CIN* refer respectively to the onset of the QRS, the start of the carotid upstroke, and the carotid incisural notch. The initial weight (*B*) caused a pronounced increase in the degree of systolic outward motion (upstroke) in both subjects. This is possibly to be ascribed to partial counterbalance of the stiffness of the intercostal membranes (see text). As additional weight was added (*C*), the systolic outward excursion again increased in both subjects, Subject II because the sensitivity of the recording apparatus had been reduced. Thus, the mass × distance lifted was much greater for both subjects in *C* than in *B*. But when still more weight was added (*D*), the magnitude of the systolic outward movement decreased slightly. Thus, in both subjects the product, mass × distance, was about the same in *D* and in *C*. But because of the reduced recording sensitivity the actual distance that the same weight was lifted (wasted work) was about three times as great in the patient as in the normal subject.

sistance to such displacement. It is probable, therefore, that the correct explanation is one of the last two or a combination of them. Furthermore, the descent of the weight in late systole could facilitate ejection and thereby reduce wasted work, only if the first possibility were true. But in that case one would expect the weight on the chest wall to be associated with an increase in stroke volume or other hemodynamic changes. That these were not found is indicated below.

This discussion refers only to the left ventricle and to records from the region of the apex. Traces from the right parasternal area, where there is little or no lung anterior to the heart, may quite possibly be influenced by a direct effect of the weight in compressing the right ventricle. That is one of the reasons that this report is confined to patients with ischemic heart disease or left ventricular loads and to records secured from the region of the apex.

One may summarize these several considerations by saying that there is strong although indirect, evidence for the view that the lift of the weight as herein measured does represent a crude reflection of the wasted work of the left ventricle.

Because of the large amount of intervening lung paradoxical motions cannot be recorded from the posterolateral portions of the left ventricle. Downward bulge of the diaphragmatic surface of the left ventricle likewise cannot be registered satisfactorily One is limited to studying abnormalities of the movements of the anterolateral and apical regions. This defect in the method can only produce *false low* values for wasted work. The same is true of those patients who do not tolerate sufficient weight to achieve a work plateau. In these one can only say that the actual wasted work is at least as great as, and possibly greater than the measured value

Hemodynamic effects of weight on chest The possibility that the procedure itself may lead to artificially high values for wasted work cannot be excluded with certainty But if this were the case one would expect that simultaneous measurements of hemodynamic functions would probably display evidence of a consistent alteration in cardiac behavior during the application of the heavy weight. The results of nine comparisons in 5 subjects are shown in Table I Constant changes did not occur in heart rate, stroke volume cardiac output, or useful cardiac work. The central aortic blood pressure was sometimes unchanged but usually increased somewhat, presumably because of pain There was no indication that the procedure reduced the useful (pressure × flow) work by diverting energy to the wasted (weight lifting) work. Although the possibility that the wasted work was itself increased by the procedure cannot be excluded with certainty this seems to be improbable in view of the inconstant changes in pressure and flow and in view of the probability already mentioned that the values obtained by the method tend to be falsely low rather than high. In any case since a given weight was raised a given distance during systole there can be no doubt that at least that much work was expended under the conditions prevailing when the measurement was made. Nevertheless the failure to observe consistent alterations in the useful (pressure × flow) work during the application of the weights to the chest does not preclude with certainty the possibility that the procedure may have in some unknown manner caused a momentary exaggeration of the wasted work as herein measured But it is reasonable to believe that the results of the hemodynamic observations reduce the likelihood of such a possibility

Results

The data concerning the work involved in outward systolic movements are shown in Figs. 3 and 4 and summarized in Table II The work related to atrial contraction and to those small outward motions during ventricular systole which do not cause displacement above the diastolic base line are neglected. The chief cause of the work wasted by the normal heart is the outward motion of the recoil as ejection begins. The normal values ranged from 0 13 to 5 3 gram-meters per beat, the median being 2.5 The integrals of wasted stroke work for normal hearts varied between .07 and .37 gram-meter seconds, with a median of 23 The median normal values for wasted work per minute was 205 gram meters (range 7.2 to 640) and the median for the integral was 21 6 gram-meter seconds per minute (range, 3 9 to 32.3)

The values for the wasted stroke work in patients with ischemic heart disease were above the normal range in 18 of 23 measurements on patients with systolic bulges that could be felt or recorded The only patient without such a bulge had values well within the normal range. The figures for the integral of stroke work displayed a similar trend with an even greater difference from the normal subjects. Only three measurements were within the normal range

Table I. Hemodynamic effects of weight on chest

Subject	Age (yr.)	Diagnosis	Weight on chest (kilos)	Central art. pressure (mm. Hg) Systolic	Central art. pressure (mm. Hg) Diastolic	Heart rate per minute	Stroke volume (ml.)	Cardiac output per minute (liters)	Useful work Per beat (Gm.M.)	Useful work Per minute (Kg.M.)
J.T.	31	Aortic stenosis, aortic insufficiency	0	132	70	75	118	8.8	176	13.2
			22.7	150	84	85	141	12.0	258	21.9
H.M.	35	Chest wall pain	0	118	76	67	135	9.1	201	13.5
			22.7	118	76	68	138	9.4	205	13.9
			0	113	70	65	140	9.1	196	14.8
			0	113	70	80	144	11.5	202	16.2
			22.7	109	64	89	123	10.8	165	14.7
			0	98	62	90	114	10.3	141	12.7
G.T.	51	Angina pectoris	0	132	92	130	38	4.9	57	7.4
			22.7	172	120	133	39	5.2	77	10.1
			22.7	160	115	133	45	6.0	64	8.6
H.B.	42	Angina pectoris	0	142	90	63	75	4.7	115	7.2
			0	166	108	75	67	5.0	122	9.1
			22.7	144	110	91	52	4.7	90	8.2
			0	130	98	99	52	5.1	81	8.0
			22.7	150	110	77	58	4.5	102	7.8
			0	160	104	88	60	5.3	105	9.3
			22.7	186	110	68	74	5.0	143	9.7
			0	134	84	86	55	4.7	80	6.7
K.P.	41	Diabetes, normal heart	0	164	94	73	84	6.1	131	9.6
			22.7	158	96	75	69	5.2	115	8.7

*Calculated by assuming mean aortic systolic pressure to be diastolic pressure plus $\frac{\text{pulse pressure}}{3}$ and specific gravity of blood to be 1.055.

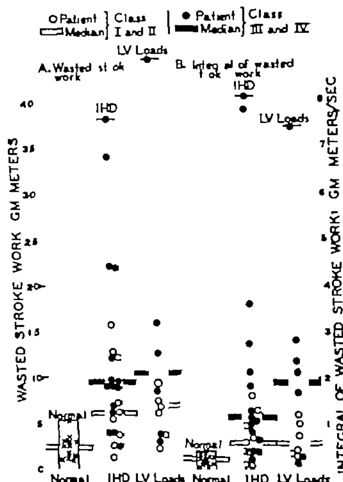


Fig. 3. Stroke work wasted in paradoxical motion. *A*. Despite the scatter the trend is toward increase wasted work with progressive functional impairment. The median value for the Class III and Class IV patients is about four times the normal, and the highest values are nearly 20 times the normal median. Because of the wide scatter the average values are not calculated. *B*. The median values for the integral of wasted work, which may be considered to represent wasted effort (*see text*) are 6 to 9 times as great in the Class III and Class IV patients as in the normal subjects. The maximal values are almost 40 times as large. The reason for the greater increase in the integral, as compared to the work, is the longer duration of the systolic outward motion in the patients than in the normal subjects. The Class I and Class II patients are intermediate in all respects. The probable reason for the low values in a few of the patients with pronounced functional impairment is the inability of the method to detect abnormal systolic motions of the posterior and inferior portions of the left ventricle. Systolic protrusion of such areas would tend, because of the change in shape, to increase the *inward* movement of the apical region and thus to produce falsely low measurements of wasted work.

whereas the majority of the values were 3 to 30 times the average normal. The wasted work per minute was within the normal range in eight and below the normal median in three of 24 measurements but above the normal range in 16 instances. The highest value was about 1 400 per cent above the normal median. The differences in regard to the integral of the wasted work per minute were again still larger, the median and the highest values being respectively about 400 and 3 100 per cent above the normal median.

Despite the wide individual variations the trend of all of the values for wasted work was toward a higher level for the patients with larger degrees (Class III and Class IV) of functional impairment as compared to those with less (Class I and Class II) impairment.

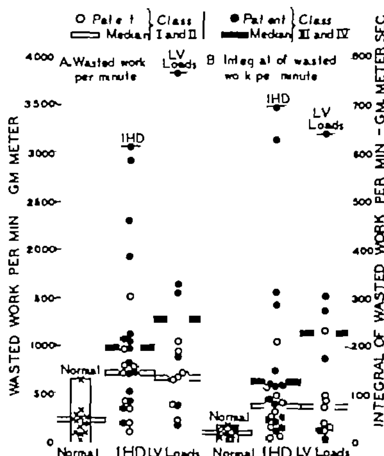


Fig. 4. Left ventricular work per minute wasted in paradoxical motions. Again we have the wide scatter with some values that are probably falsely low (see legend for Fig. 3). Despite this, the median and highest values for wasted work per minute in the Class III and Class IV patients are about 5 and 15 times the median normal measurement. Again the differences in the integrals are still greater, the median and highest values being, respectively, 8 and 30 times the median normal. The Class I and Class II patients are intermediate.

The findings in the patients with left ventricular loads were essentially similar to those in the patients with ischemic heart disease. Again there was a wide scatter but the trend was toward elevated values for wasted work per beat and per minute and for a somewhat greater increase as compared to the normal values in the integrals of these functions. Likewise, the median levels were higher in the subjects with the greater functional impairment.

Comparisons of wasted work with useful work (assumed) are shown in Table III. The median values for wasted work of Class III and Class IV patients are about 10 and 15 per cent per beat and per minute, respectively, of the useful work of the normal adult heart. But the highest values for wasted work are almost one half that of the normal useful work and may equal or exceed the reduced useful work of the heart in severe failure.

The explanation for the greater abnormality in the integral measurements than in the wasted work values lies in the increased duration of the systolic outward motion in the patients. Although in the strict physical sense the work (mass × distance) performed in chinning oneself on a horizontal bar is the same whether one holds the position for a second or a minute, any school boy is aware of the difference in the effort required.

A distinction should be drawn between the ejection work and the useful work. The former can be calculated if one knows the left ventricular pressure and the *total*

stroke volume which in a patient with aortic or mitral regurgitation is not the same as the *measured* stroke volume. Thus in such patients the useful work (mean aortic pressure × measured stroke volume) is less than the ejection work. Similarly in a patient with severe aortic stenosis the ejection work may far exceed the useful work (Table III Subjects C W and M T) because of the pronounced pressure gradient.

In those patients who were subjected to cardiac catheterization it was possible to compare the useful work of the left ventricle with the wasted work of the systolic bulge. Such comparisons are shown in Table III It should be noted that there were 2 patients (J G and P Q) who had grossly increased stroke work (as compared to an average normal value of about 100 gram meters) but no evidence of impaired efficiency in terms of excessive work wasted by systolic protrusion of the precordium Both of these patients were asymptomatic. In the 3 Class III patients the wasted work of the left ventricle was a significant fraction—one fourth to one third—of its useful work.

The inefficiency—as herein roughly measured in terms of wasted work—seems to parallel the clinical state more closely than the performance in terms of output or stroke work (Table III) Thus each of the Class III patients had an increase in wasted work but the reduction in output and in stroke work was inconstant.

No data concerning the patients with ischemic heart disease are included in Table III because none of them was catheterized

Discussion

Before certain implications of the data are considered the crudeness of the method should be re-emphasized Aside from the possible sources of error that have already been cited under *Critique of method* the measurements were made in acute experiments and do not reflect such adaptation as might occur in the heart during a period of months or years. Furthermore the procedure of placing weights over the precordium is highly artificial and represents a type of load that is different from any occurring during the natural history of cardiac disease Likewise it is highly improbable that the values for wasted work are quantitatively accurate Reasons why the method as herein employed probably yields false low values have been cited but the degree of error remains unknown In any case the data indicate that in patients with pronounced functional impairment the work wasted in outward motion of the apex is no less than one fourth to one third of the useful work (Table III) and may actually equal the useful work of a patient in severe heart failure (Table II) These findings are in rough accord with the observation of Tyson and associates concerning the functional impairment of dogs with paradoxical movements of artificial ventricular aneurysms.

The observations are in keeping with the bedside observation of a general parallelism between the gravity of the clinical state and the size—both in amplitude and area—of the palpable systolic outward motion.

The analogy already cited to chinning a horizontal bar illustrates that when the position is sustained the effort expended may be much greater than the work done. Thus, the median values for wasted stroke work and wasted work per minute of the Class III and Class IV patients were four to six times as great as those of the healthy subjects. But the medians for the *wasted effort* i.e. the integral of wasted work were six to ten times as large as the normal. In extreme instances (Figs. 3 and 4) the wasted work was fifteen to twenty times the normal and the wasted effort was twenty to forty times the median normal The patients with slight or no functional impairment were intermediate in all respects.

During the past two decades, studies of pressure and flow in man have been of tremendous diagnostic value and have also advanced our concepts concerning the precise hemodynamic distortions caused by various mechanical lesions. Cardiac catheterization as usually carried out provides important information about *performance* i.e., about what the heart *does* But it tell us little about *efficiency* i.e. about what the heart *does not do* and how *it fails to do it* These statements are not made to belittle a valuable method but only to emphasize

Table II Wasted work Summary of findings

	Group	Subgroup	Stroke work (gram-meters) Highest	Lowest	Median
Wasted work	Normal		5 3	13	2 5
	Ischemic heart disease	Classes I and II	15 8	1 3	6 5
		Classes III and IV	38 3	2 3	9 5
	Left ventricular loads	Classes I and II	11 2	2 5	7 0
		Classes III and IV	44 5	3 3	10 5
Approximate useful (flow × pressure) work	Normal				100
	Severe heart failure				40

*Calculated by assuming stroke volumes of 75 and 80 ml heart rates of 75 and 110, duration of ejection of 28 and 16 second, respec

Table III Wasted work and useful work in patients with left ventricular loads

Subject	Age (yr.)	Sex	Diagnosis	Class	Heart rate	Stroke volume (ml.)	Mean LV and aortic systolic pressure (mm. Hg)	Stroke work (gram-meters) Ejection	Useful (USW)	Wasted stroke work (WSW) Gram-meters	WSW/USW (%)
M C	31	M	PDA	I	66	82	103	121	121	4 5	3 5
D L.	21	M	AI	I	71	93	88		>117	11 3	9 7
J G	18	M	AS	I	80	138	107 86	211	170	4 7	2 8
P Q	19	F	AS	I	78	73	154 78	165	84	4 0	4 8
J D	17	M	AS	II	87	97	90 69	125	96	9 5	9 9
B.T	42	M	AI	II	70	84	121		>144	14 6	10 1
C.W	28	M	AS	III	76	78	240 81	268	90	21 8	24 2
M T	39	F	AS	III	82	52	224 79	167	59	17 3	29 3
E.G	24	M	AI	III	60	55	188		>143	44 5	31 1

*Cannot be calculated because the regurgitant flow is unknown
PDA Patent ductus arteriosus. AI Aortic insufficiency AS Aortic stenosis

that it like every other procedure has its limitations.

These considerations point to the conclusion that some of the prevailing concepts of ventricular behavior are based on oversimplifications. Thus the idea that at any given moment a Starling (function) curve of a ventricle reflects the state of all of the fibers of that ventricle is incompatible with the condition of a chamber which has not only healthy but also infarcted and intermediate (ischemic) areas, each of which

Integral of stroke work (gram meter seconds)			*Work per minute (gram-meters)*			*Integral of work per minute (gram-meter seconds)*		
Highest	*Lowest*	*Median*	*Highest*	*Lowest*	*Median*	*Highest*	*Lowest*	*Median*
37	07	23	640	7 2	205	32 3	3 9	21 6
2 2	16	65	1 531	116	730	210	14 1	75 0
8 1	26	1 2	3 061	196	975	696	33 3	125
2 1	31	60	1 045	233	675	235	29 1	75 0
7 5	22	1 9	3 830	185	1 275	641	7 9	225
		28			7 500			2 100
		7 2			4 400			792

tively for normal and for severe heart failure. Mean systolic aortic pressure assumed to be 94 mm Hg for both.

has a different curve.[1] The same difference probably applies to the enlarged heart which has some areas that protrude and others that shorten during systole Such reservations do not negate the great merit of function curves as a research method but only imply that they yield incomplete, although valuable information

The term *cardiac asynergy* has been used[8] to designate a state of disordered teamwork between the different areas of the same organ and the more specific phrase *intraventricular asynergy* to signify poor coordination between different muscle fibers of the same ventricle. Since however a complete absence of such teamwork is observed only in the presence of ventricular fibrillation the expression *dyssynergy* is to be preferred The dyssynergic effect of expansile systolic protrusions, whether due to ischemia or enlargement or both is obvious. The healthy areas are faced with the double task of expelling blood not only into the great arteries but also into the bulge The fiber shortening due to the change in shape reduces the contractile strength available for the change in volume Presumably such a reduction in what might be called effective contractile strength will ultimately favor the development of congestive failure in patients who would not be considered by the usual criteria to be likely candidates for it.

During recent years there have been numerous reports of beneficial results after resection of postinfarctional *anatomic ventricular aneurysms* One wonders whether a surgical *attack on these functional aneurysms* i.e. areas which balloon outward only under the stress of systolic pressure would be fruitful Possibly practical methods may be developed for applying prostheses that limit systolic expansion of the involved areas, without the necessity of the more hazardous procedures of cardiac bypass and of myocardial resection. These thoughts are offered not to encourage immediate clinical application but in the hope that they may stimulate the extensive animal experimentation that should precede any such application

There is general agreement that heart failure whether in the heart-lung preparation[17] in the dog with acute failure[18] or chronic failure due to induced valvular disease or in man[18] is characterized by a decline in the ratio

$$\frac{\text{Useful work}}{\text{Myocardial oxygen consumption}}$$

The data herein reported suggest that *one* of the mechanisms responsible for such a

reduction in efficiency of the left ventricle is the wasted work involved in paradoxical systolic motion. This is not the only mechanism because there is evidence of a change in the contractility of actomyosin bands prepared from failing hearts. Another mechanism is an increase in the ejection work (*total* stroke volume × mean *left ventricular* systolic pressure) without a corresponding rise in the useful work (*measured* stroke volume × mean *aortic* systolic pressure). Such a distortion obviously occurs in patients with mitral insufficiency and in those with aortic insufficiency or stenosis. Regardless of such factors dilatation per se tends to cause mechanical inefficiency because more work is obviously required during isovolumic contraction to lift 300 ml than 200 ml of blood to the level of aortic diastolic pressure. Thus if the stroke volume and other factors remain constant, the dilated ventricle is inherently less efficient. In any case the data indicate that the dyssynergic effects of abnormal systolic movements associated with ischemic heart disease and with left ventricular overloads are, in some patients of a magnitude sufficient to play an important role in reducing ventricular efficiency.

Summary

An attempt has been made to determine the wasted cardiac work involved in paradoxical outward motions of the precordium. The upward displacement during systole of a known weight placed on the apical area has been measured in (a) persons with normal hearts, (b) patients with ischemic heart disease and (c) patients with disorders that place an increased load on the left ventricle. Reasons for the opinion that *the values obtained for wasted left ventricular work a e falsely low* have been cited. The procedure did not cause consistent changes in useful cardiac work, which was serially measured in a few subjects with and without the weights on the chest.

In the normal control subjects the levels for wasted work varied between 0.1 and 5.3 gram meters per beat, and the median was about 2.5 per cent of the normal useful (pressure × flow) work of the left ventricle. The data for patients who in the absence of a precordial weight, had normal tracings of chest wall motion (kinetocardiograms) were usually within the normal range or only slightly above it. The patients who without added weight displayed paradoxical motion had values for wasted work of 5 to 45 gram meters.

Calculations were also made of the wasted stroke effort, i.e. the integral of the wasted work. The range and median for the subjects with normal hearts were 0.7 to 3.7 and 2.3 gram meter seconds respectively. Again some of the patients were within the normal range but those with pronounced systolic outward motion had values that were markedly elevated and up to more than 30 times the normal median.

Cardiac catheterization was performed in 9 of the 13 patients who had lesions that caused left ventricular overloading. In 6 of these subjects the wasted stroke work exceeded 9 per cent of the useful work (mean aortic pressure × measured stroke volume) and in 3 the wasted work was more than 24 per cent of the useful work of the same subject. The highest value found was 44 per cent of the normal value of 100 gram-meters per beat and 31 per cent of the patient's left ventricular useful stroke work. Calculations from the data suggest that in some patients with severe heart failure the work wasted in paradoxical systolic movements may equal the useful work.

In patients at rest the cardiac inefficiency as judged by wasted work appeared to parallel the clinical state more closely than did the cardiac performance as judged by useful work.

It is concluded that in some patients the work wasted in causing paradoxical systolic motion is sufficient to cause pronounced impairment of myocardial efficiency. The term *ventricular dyssynergy* is applied to this condition in which a portion of the energy generated by some of the fibers is diverted to stretching others. Some possible implications of this concept are discussed. Chief among them is the realization that although knowledge of the *performance* (pressure and flow) of a given heart is very helpful additional information concerning *efficiency* is essential for complete evaluation of its *functional* state.

REFERENCES

1. Coghlan, C., Prieto, G., and Harrison, T. R.: Movements of the heart during the period between the onset of ventricular excitation and the start of left ventricular ejection, Am. Heart J. 62:65, 1961.
2. Prieto, G., Coghlan, C., and Harrison, T. R.: Movements of the heart during the period between the onset of relaxation and the beginning of ventricular filling, Am. Heart J. 6 :528, 1961.
3. Harrison, T. R., Coghlan, C., and Prieto, G.: Movements of the heart during ejection, Am. Heart J. 62:804, 1961.
4. Harrison, T. R., and Hughes, L. M.: Precordial systolic bulges during anginal attacks, T. A. Am. Physicians 1 174, 1958.
5. Suh, Soon Kyu, Cooper, W. H., Frederick, W., and Eddleman, E. E., Jr.: Force, work and power ballistocardiography, Am. J. Cardiol. 1:726, 1958.
6. Davie, J. D., Langley, J. O., and Eddleman, E. E., Jr.: Clinical and kinetocardiographic studies of paradoxical precordial motions, Am. Heart J. 63:775, 1962.
7. Tennant, R., and Wiggers, C. J.: Effect of coronary occlusion on myocardial contraction, Am. J. Physiol. 112:351, 1935.
8. Murray, G.: Pathophysiology of cause of death from coronary thrombosis, Ann. Surg. 126:523, 1947.
9. Tyson, K., Mandelbaum, I., and Schumacher, H. B., Jr.: Experimental production and study of left ventricular aneurysms, J. Thoracic & Cardiovas. Surg. 44:731, 1962.
10. Harrison, T. R.: Some unanswered questions concerning enlargement and failure of the heart (Grady Reddick lecture), Am. Heart J. 69:100, 1965.
11. Jones, W. B., Russell, R. O., Jr., and Dalton, D. H., Jr.: An evaluation of computed stroke volume in man, Am. Heart J. 72:746, 1966.
12. Starling, E. H., and Visscher, M. D.: The regulation of the energy output of the heart, J. Physiol. 62:243, 1927.
13. Harrison, T. R., Friedman, B., and Resnik, H., Jr.: The mechanism of acute experimental heart failure, Arch. Int. Med. 57:927, 1936.
14. Olson, R. E., Ellenbogen, E., and Iyengar, R.: Cardiac myosin and congestive heart failure in the dog, Circulation 24:471, 1961.
15. Danforth, W. H., Ballard, F. B., Kako, K., Choudhury, J. D., and Bing, R. J.: Metabolism of the heart in failure, Circulation 21:112, 1960.
16. Bing, R. J., and Kako, K.: Contractile proteins of heart muscle in man, Circulation 24:483, 1961.

The hemodynamic effect of slowing the heart rate by paired or coupled stimulation of the atria

John H. Lister M.D.
Anthony N. Damato M.D. *
Bernard D. Kosowsky M.D.
*Sun H. Lau M.D.****
Emanuel Stein M.D. *
Staten Island, N. Y.

It has been shown that coupled and paired pacing of the ventricles or atria can slow the mechanical heart rate.[1] During paired or coupled stimulation of the ventricles there are two electrical depolarizations for each mechanical contraction. This phenomenon not only slows the mechanical heart rate but also results in postextrasystolic potentiation (PESP),[1] a marked increase in the force of contraction of the heart. Although PESP markedly increases the contractility and oxygen consumption[1-4] of the myocardium, it has not been shown to increase cardiac output in man or the intact animal.[-4] The abovementioned combination of effects of PESP will probably limit the clinical use of paired or coupled stimulation of the heart primarily to the control of rapid heart rates.

Langendorf and Pick[5] published a record which showed that the heart rate had been slowed by coupled stimulation of the atria. Each pair of atrial depolarizations was followed by a single ventricular depolarization. The second of each of a pair of atrial impulses was blocked at the atrioventricular node. Slowing the heart rate without altering ventricular activation or the state of the patient should result in a diminished myocardial oxygen consumption.[1] Consequently, coupled or paired stimulation of the atria with a single normal ventricular response should be of clinical importance in the control of rapid sinus heart rates provided that cardiac output is maintained.

The purpose of this study was to investigate the effect on cardiac output and peripheral pressure of slowing the heart rate by paired or coupled stimulation of the atria associated with a single normal ventricular depolarization.

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
Supported in part by National Institutes of Health Grant No. CD-00089 and No. HE 09156-01 and Bureau of Medical Services, Division of Hospitals, U.S.P.H.S. Grant No. F-66-29.
Received for publication May 26, 1966.
*Consultant in Cardiology, U.S.P.H.S. Hospital, Staten Island, N. Y.; Research Associate, Department of Pharmacology, College of Physicians & Surgeons, Columbia University, New York, N. Y. Present address: Cardiac Catheterization Laboratory, Montefiore Hospital and Medical Center, 111 East 210th St., Bronx, N. Y. 10467.
**Director, Cardiopulmonary Laboratory, U.S.P.H.S. Hospital, Staten Island, N. Y.
***Bureau of State Services Cardiovascular Fellow, Cardiopulmonary Laboratory, U.S.P.H.S. Hospital, Staten Island, N. Y.
****Assistant Chief, Cardiopulmonary Laboratory, U.S.P.H.S. Hospital, Staten Island, N. Y.
*****Deputy Chief, Cardiopulmonary Laboratory, U.S.P.H.S. Hospital, Staten Island, N. Y.

Table I. Clinical state of patients studied

Case number	Age (yr.)	Clinical state	Drug therapy
1	48	Post-cardioversion, cancer of lung	Quinidine, digitalis
2	60	Post-cardioversion, chronic lung disease	Quinidine, digitalis
3	43	Normal	None
4	41	Wolff-Parkinson-White syndrome	None
5	56	Post-cardioversion, arteriosclerotic heart disease	Quinidine, digitalis
6	65	Post-cardioversion, arteriosclerotic heart disease, old myocardial infarction, anterior papillary muscle syndrome, congestive heart failure	Quinidine, digitalis
7	71	Post-cardioversion, arteriosclerotic heart disease, congestive heart failure	Quinidine, digitalis
8	39	Rheumatic heart disease, moderate mitral stenosis	Digitalis
9	49	Arteriosclerotic heart disease, rheumatic heart disease, mild aortic stenosis	Digitalis
10	39	Congestive heart disease, moderate pulmonary stenosis	Digitalis
11	42	Congestive heart disease, ventricular septal defect	Digitalis

Methods

Studies on 11 patients who ranged in age from 39 to 71 years form the basis of this report (Table I). All subjects were in sinus rhythm at the time of study. A right heart catheterization was performed under local anesthesia using an antecubital vein. Under fluoroscopic and electrocardiographic control a No. 8 single-lumen catheter was advanced into the pulmonary artery. Similarly, a bipolar electrode catheter was positioned in the right atrium. The position of the electrode catheter was confirmed by recordings of characteristic intracardiac electrograms. A brachial artery was cannulated with a Cournand needle. The bipolar electrode catheter was connected to a battery-powered (Medtronic) external paired pacemaker. Pulmonary and brachial arterial pressures were recorded by means of P23d Statham strain-gauge transducers (leveled 5 cm. below the sternal angle). Cardiac outputs were determined in duplicate by the dye-dilution technique using indocyanine green dye.

Cardiac outputs and brachial and pulmonary arterial pressures were obtained at sinus rhythm during single pacing of the atria above the sinus rate and during paired or coupled pacing of the atria below the sinus rate. The interval between the stimuli of each of a pair of atrial impulses was 280 to 310 msec. The strength of intensity used for pacing was approximately twice threshold.

All records were taken on a multichannel oscilloscopic photographic recorder. Careful attention was paid to the proper grounding of all equipment, in order to avoid random currents from initiating atrial fibrillation.

Results

In 10 of the 11 subjects paired and/or coupled stimulation of the atria resulted in an effective slowing of the ventricular rate without an associated alteration in ventricular activation (Fig. 1). For each two atrial impulses there was a single ventricular electrical event; the second of each of a pair of atrial impulses was blocked at the atrioventricular node.

In the one exception (Case 10) it was not possible to block the second of each of a pair of atrial impulses. Coupled and paired atrial pacing resulted in 1:1 atrioventricular conduction (Fig. 2). When the interval between each of a pair of pacemaker impulses was further reduced, the second of each of a pair of impulses no longer captured the atria. The arterial pressure tracing in Fig. 2 shows that the effective mechanical heart rate was slowed by paired and coupled pacing of the atria. For each two ventricular depolarization there was a single effective mechanical contraction; the second of each of a pair of ventricular depolarizations resulted in a second mechanical ventricular response during which the intraventricular pressure

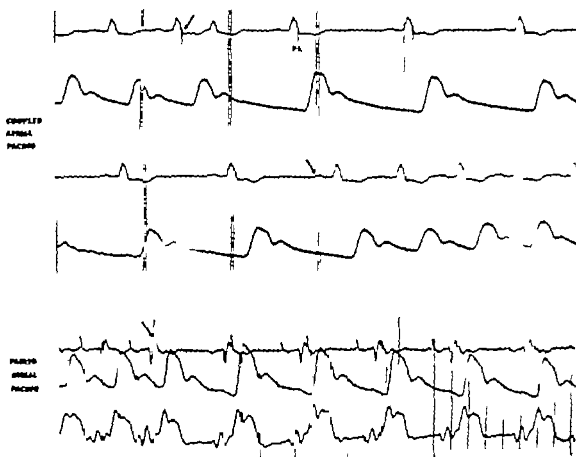


Fig. 1. Slowing of the electrical and mechanical ventricular rate by coupled and paired stimulation of the atria. *Strips 1* and *2*. Simultaneous Lead II electrocardiogram and brachial arterial pressure tracing. The second normal sinus beat is followed by a paced coupled atrial beat which is conducted to the ventricle and has a markedly prolonged P-R interval. The next two coupled atrial beats are blocked at the A-V node and both the electrical and mechanical ventricular rates have been reduced by 45 per cent. The arrow in *Strip 1* shows where the pacemaker was turned on and the arrow in *Strip 2* shows where the pacemaker was turned off. After coupled atrial pacing is discontinued, there is immediate reversion to a more rapid regular sinus rhythm. *Strip 3*. Simultaneous Lead III electrocardiogram and brachial arterial and right ventricular pressure tracings during paired atrial pacing. The first beat is a single paced beat of the atria. The arrow shows the initiation of paired atrial pacing. Both the electrical and mechanical ventricular rates are halved from the beat following the first paired paced beat. The interval between each of a pair of atrial impulses is 290 msec. Paper speed 100 mm. per second; time lines in *Strips 1* and *2*, 1 sec.; time lines in *Strip 3*, 0.2 sec. P.I., Pacemaker impulses.

that was developed was inadequate to open the semilunar valves. The brachial arterial pressure pulse in Fig. 2 also shows the effect of PESP: the upstroke velocity was increased and the ejection time was shortened.

Table II shows the hemodynamic results of decreasing or increasing the heart rate by atrial pacing. There was no significant change in cardiac index (CI) when the heart rate was decreased below the sinus rate as much as 45 per cent or increased above the sinus rate as much as 50 per cent (Fig. 3). The stroke index (SI) was inversely related to the heart rate (Fig. 4). There was an almost linear relationship between heart rate times blood pressure and heart rate (Fig. 5).

Discussion

In most patients with sinus rhythm the electrical and mechanical rate of the ventricles can be slowed by paired and coupled pacing of the atria. The second of each of a pair of atrial impulses is blocked at the atrioventricular node. Langendorf and

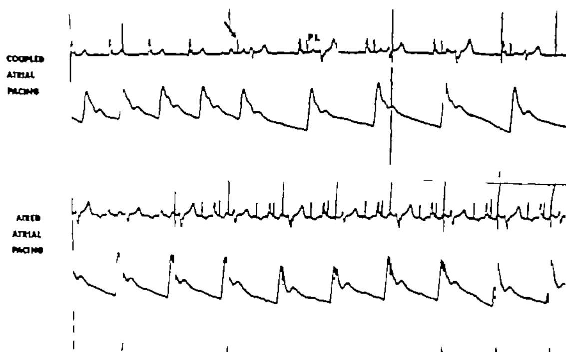


Fig. 2. Postextrasystolic potentiation resulting from coupled and paired stimulation of the atria (Case 10). *Strip 1.* Simultaneous Lead II electrocardiogram and brachial arterial pressure pulse tracing. The first five beats are regular sinus rhythm. The arrow shows where coupled atrial pacing was initiated. Each coupled paced atrial beat is followed by a prolonged P-R interval and conducted aberrant ventricular response. The effective mechanical heart rate is slowed. For each two ventricular depolarizations there is a single effective ventricular mechanical contraction. The brachial arterial pressure pulse shows the effect of postextrasystolic potentiation. There is an increase in the rate of rise of the brachial arterial pressure pulse and the ejection time is shortened. *Strip 2.* Paired atrial pacing resulting in postextrasystolic potentiation. Each atrial impulse is followed by a ventricular response. The second of each of pair of impulses is followed by a prolonged P-R interval and an aberrant ventricular response. For each two ventricular electrical events there is a single effective ventricular contraction. The brachial arterial pressure pulse shows that the effective mechanical heart rate has been slowed and the effects of postextrasystolic potentiation are seen. The interval between the impulses of an atrial pair is 280 msec. Paper speed 50 mm. per sec.; time lines 1 sec.

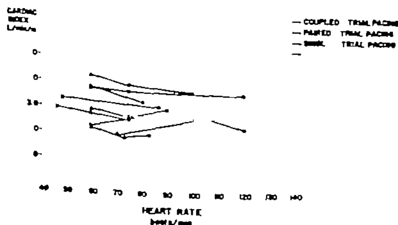


Fig. 3. Relationship of cardiac index (CI) to heart rate. There is no significant change in cardiac index when the heart rate is decreased below the sinus rate as much as 45 per cent or increased above the sinus rate as much as 50 per cent.

Table II Hemodynamic data

Case number	Rhythm	HR	CI	SI	BA	BAM	HR × BP
1	PAP	70	1 95	27 9	155/80	105	7 350
	RSR	105	2 64	25 1	155/90	120	12 600
	SAP	120	2 23	18 6	140/90	110	13 200
2	PAP	60	2 30	38 0	100/38	50	3 000
	RSR	80	2 70	33 7	105/40	60	4 800
	SAI	120	2 65	22 1	100/50	65	7 800
3	PAP	60	4 60	76 6	140/75	105	6 300
	RSR	90	4 60	51 7	130/80	105	9 400
	SAP	130	4 69	36 1	125/95	105	13 650
4	PAP	60	3 75	62 5	90/60	75	4 500
	RSR	75	3 65	48 7	115/70	80	6 000
	SAP	120	3 56	29 6	110/70	80	9 600
5	PAP	60	3 74	62 3	200/70	110	6 600
	RSR	80	3 27	40 4	200/75	110	8 800
6	PAP	60	2 24	37 3	140/60	88	5 280
	RSR	75	1 85	24 6	130/55	80	6 000
	SAP	85	2 01	24 1	135/65	87	7 395
7	PAP	60	1 66	27 6	118/60	85	5 300
	RSR	75	1 52	20 2	125/65	90	6 750
	SAP	90	1 67	18 5	118/70	85	7 650
8	PAP	65	4 26	65 5	125/65	75	4 875
	RSR	75	3 89	51 8	120/65	85	6 375
	SAP	100	3 64	36 4	115/70	85	8 500
9	CAP	48	3 32	69 1	140/45	70	3 360
	RSR	87	3 04	34 9	130/65	90	7 830
10.	CAP*	46	2 94	63 9	170/75	100	—
	PAP*	60	2 74	45 7	160/70	110	—
	RSR	75	2 55	34 0	145/85	105	—

*In Case 10, during paired and coupled stimulation of the atria there was 1 1 A-V conduction which resulted in postextrasystolic potentiation

Case 11 has been omitted because there was [illegible] left-to-right shunt, and the cardiac output was not calculated. *RSR* Regular sinus rhythm. *SAP* Single atrial pacing *PAP* Paired atrial pacing *CAP* Coupled atrial pacing *HR* Heart ra[illegible] *CI* Cardiac index (L./min./M.²) *SI* Stroke index ([illegible] c./min./M.²) *BA* Brachial arterial pressure (mm. Hg) *BAM* Mean brachial arterial pressure *HR × BP* Heart rate [illegible] mean arterial blood pressure.

Pick[9] originally showed this phenomenon in one patient.

In man during paired and coupled atrial pacing the second of a pair of atrial impulses is usually blocked at the atrioventricular node, because the refractory period of the A V node is normally longer than the refractory period of the atrial myocardium.[11] In Case 10 it was not possible to adjust the interval between the stimuli of a pair of atrial impulses so that the second impulse would be blocked at the A V node. In this instance the refractory period of the A V node was as short as or shorter than the refractory period of the atrial myocardium. In this patient paired and coupled stimulation of the atria resulted also in paired and coupled stimulation of the ventricles. The effective mechanical heart rate was slowed and the effects of PESP were present.

No arrhythmias were encountered during

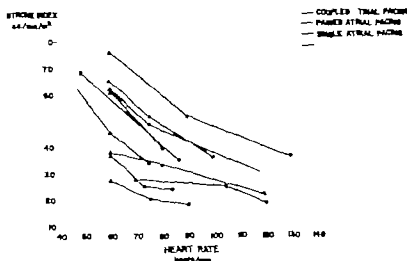


Fig. 4 Relationship of stroke index (SI) to heart rate. There is an inverse relationship between SI and heart rate.

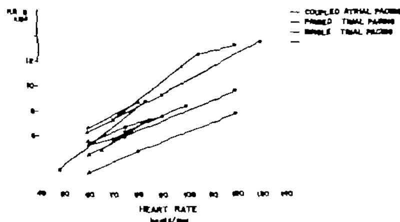


Fig. 5 Relationship of heart rate times blood pressure to heart rate. There is close to linear relationship between heart rate times blood pressure and heart rate. *H.R. × B.P.* Heart rate times mean arterial blood pressure.

paired or coupled stimulation of the atria. We were careful not to place the second of a pair of atrial impulses into the vulnerable period of the atrium. The interval between atrial impulses of a pair was maintained between 280 and 310 msec. When there is a 1:1 atrioventricular response during paired or coupled pacing of the atria, the vulnerable period of the ventricle is avoided because atrioventricular conduction time is prolonged for the second beat of a pair. Paired and coupled pacing of the atria is a safe and reliable method for slowing the heart rate in patients with sinus rhythm.

Ross and his associates[13] and Stein and his associates[14] recently reported on the hemodynamic effects in man of increasing the heart rate above the sinus rate by electrical stimulation of the right atrium. These investigators showed that there was no significant change in cardiac output when the heart rate was increased above the sinus rate. Our results are in agreement with their findings.

Up to the present time there have been no reports in the literature on the hemodynamic effects of slowing the heart rate without an associated alteration in ventricular activation. However, hemody-

namic studies have been reported in which the heart rate was slowed by paired and coupled stimulation of the ventricles.[1-8] In man and the intact animal paired and coupled stimulation of the ventricles does not significantly alter cardiac output [4] but it does increase myocardial oxygen consumption

Katz has shown that heart rate times arterial blood pressure is a rough index of myocardial oxygen consumption provided that ventricular activation is unchanged the state of the patient is constant and the ventricular end-diastolic volume is not appreciably altered In this study it may be presumed that when the heart rate was reduced by paired and coupled pacing of the atria, myocardial oxygen consumption was probably diminished since the product of heart rate times blood pressure was reduced and cardiac output was unchanged The changes in myocardial oxygen consumption when the heart rate is reduced by paired and coupled pacing of the atria with a single normal ventricular response remain to be verified by direct measurements

The results of this study show that, when the heart rate was decreased by as much as 45 per cent below the sinus rate there was no significant change in the external work of the heart cardiac outputs and mean arterial pressures were not significantly altered Apparently there are homeostatic mechanisms which maintain cardiac output close to a constant level while heart rates are varied over a wide range.

Summary

The effect on cardiac output and arterial pressure of slowing the heart rate below the sinus rate by paired and coupled stimulation of the atria and of increasing the heart rate above the sinus rate by single pacing of the atria, was tested in 11 patients. When the heart rate was slowed by *coupled or paired stimulation* of the atria the second of each of a pair of atrial impulses was blocked at the A-V node and ventricular activation was unaltered In patients with sinus rhythm coupled and paired stimulation of the atria is a safe method for slowing the heart rate.

There was no significant change in the external work performed by the heart when the heart rate was *decreased* below the sinus rate as much as 45 per cent or increased above the sinus rate as much as 50 per cent.

REFERENCES

1. Katz, L. N. Effects of artificially induced paired and coupled beats, B ll. New York Acad. Med. 41:428 1965
2. Chardack, W M Gage, A A., and Dean D C. Paired and coupled lectrical timulation of the heart, Bull New York Acad. Med. 41:462, 1965
3. Ross, J J Sonnenblick, E H., Kaiser G. A F ommer P L., nd Bra nwald, E. Electroaugmentation of ventricular performance and oxygen consumption by repetiti applicatin of paired electrical timuli, Circulation Res. 1:332, 1965
4. Braunwald, E Ross, J J Sonnenblick, E. H., Frommer P L., Brau wald, N S and Morrow A. G Slowing of the heart rate, electroaugmentation of the heart, and increase of myocardial oxygen consumption produced by paired electrical stim lation, Bull. New York Acad. Med. 41:481 1965.
5. Braunw ld, E. Ross, J J F ommer P L., Williams, J F Sonnenblick, F H nd Gault, J H. Clinical observations on paired electrical stimulation of the heart, Am J Med. 37 700 1964
6. Chardack, W M Gage, A. A., and Dean D C Slowing of the heart by paired pulse pacemaking Am J Cardiol. 14:374 1964.
7. Singer D H Galat, G. and Wagner M L. Effects of sustained paired stim lation of the heart in normal dogs and dog following coronary artery ligation, Bull New York Acad. Med. 41:652 1965
8. Lister J W Stein, E Lau, S H. Kosowsky B D Stam, R. F and Damato, A N Post extrasystolic potentiation in th acute and chronic dog and report of one case at open heart urgery Bull New York Acad Med. 41:688, 1965
9. Langendorf R., and Pick, A Observations in the clinical use of paired electrical stim lation of the heart, Bull. New York Acad. Med. 41:462 1965.
10. Hoffman B F Bindler E nd Suckling F E. Postextrasystolic potentiation of contraction in cardiac muscle Am. J Physiol 185:95 1956.
11. Katz, L. N Recent concepts of the performance of the heart, Circulation 28 117 1963.
12. Hoffman, B. F and Cranefield, P F Electrophysiology of the heart, New York, 1960, McGraw Hill Book Co Inc.
13. Ross, J J Linhart, J W and Braunwald, E. Effects of changing heart rate in man by electrical stimulation of the right trium. Studies t rest, during exercise and with isoproterenol, Circulation 32:549 1965
14. Stein, E., Damato, A. N Kosowsky B. D Lau, S. H. and Lister J W The relation of heart rate t cardiovascular dynamics: Pacing by trial electrodes, Circulation 33:925, 1966

Case reports

Pseudocoarctation of the aorta with bicuspid aortic valve and kinked left subclavian artery: A possible cause of subclavian steal

S Lockaya M.D
B Kaplan M.D
A B Shaffer M.D
Chicago Ill

Primary kinking of the aortic arch was first reported in detail by Souders and associates in 1951 They referred to it as a subclinical form of coarctation of the aorta since there is the roentgenographic appearance of coarctation but no specific hemodynamic consequences. In the same year Dotter and Steinberg[3] also described the abnormality as did Robb. Steinberg in a subsequent publication[4] proposed the term "pseudocoarctation of the aorta. Since then nearl 60 cases have been reported in the English literature variously as subclinical coarctation pseudocoarctation mild coarctation "atypical coarctation buckl ng of the aortic arch and kinking of the aortic arch -[8]

The present case report concerns a patient whose presenting symptoms and clinical features suggested aortic valvular disease and left subclavian steal syndrome Ascending aortography disclosed a bicuspid aortic valve with mild aortic insufficiency and kinking of the distal aortic arch (pseudocoarctation) as well as of the proximal portion of the left subclavian artery

Case report

I \ 50-year-old whit woman as referred for study because of the following complaints (1) mild nonprogressi effort dyspnea of about 2 years duration, (2) two episodes of syncope within 1 month prior to admission and (3) frequent dizziness and "lightheadedness. Detailed questioning revealed that the syncope and dizziness as rule followed exercise of the left upper extremity A heart murmur had been detected 12 years previously There was no history of convulsi seizures, acute rheumatic fever or chest pain.

Pertinent physical findings included blood pressure in the right arm, 140/80 mm. Hg and blood pressure in the left arm, 120/70 mm. Hg; blood pressure in the right leg, 150/85 mm. Hg The left brachial pulse was weaker than the right. There were forceful carotid and femoral pulses bilaterally a Grade 3/6 ejection murmur t the aortic area, Grade 2/6 early diastolic blow at Erb point, and thrill due to loud systolic bruit in the left supraclavicular area, which was of greater intensity tha was the murmur over the aortic area. There was no time lag between femoral and right brachial arterial pulses The rest of the examination was unremarkable.

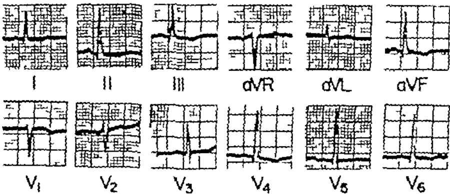
Hemogram, urinalysis, blood serology fasting serum glucose and blood urea nitrogen were normal. The initial electrocardiogram (Fig 1) showed nonspecific T-w abnormalities. These alterations regressed considerably and ectorcardiogram obtained later was considered t be withi normal

From he Cardiovascular Institute, and the Division of Cardiovascular Diseases, Department of Medicine Michael Reese Hospital and Medical Center Chicago, Ill.

This ork was supported by Grants HT-06375 and HTS-5252 from the National Heart Institute nited States Public Health Service

Received for publication April 27 1966

*Special Post-doctorate Trainee, United States Public Health Service (Grant HTS-525 he Cardiovascular Institute)
Address: Cardiovascular Institute, Michael Reese Hospital and Medical Center 29th St and Ell Ave., Chicago Ill 6061



I g 1 1 l lead elect ocardiogram obtained on dmission Described in text.



Fig. 2 Posteroanterior chest oentgenogram ith barium esophagram. Note the pparent high aortic knob nd the double shadow in this region. Further described in text.

limits. An lectroencephalogram was w thin normal limits. Chest x-ray examination nd fluoroscopy (Figs. and 3) showed that the heart size as normal. N val lar calcification as noted. A double shadow *in the region of the aortic arch* as seen to pulsate with the heart, and t indentations of the barium-filled esophagus ere noted. The aorta was elongated and tortuous. The bove-mentioned double shadow was suggesti of coarctation of the aorta, however there wa no rib notching.

Retrograde left heart catheterization as then performed order t view the aortic valve nd t delineat the nature of the mediastinal shadows. The catheter introduced in retrograde fashion via percutaneous puncture of the right femoral artery took t tating ourse t the upper end of the descend ng aorta and could not be maneuvered across the arch but the left ventric le as entered with ease ia perc taneous retrograde right brachial arterial pproach. Ascending nd descending aortic pressure pulses ere similar and were unremarkable in level or ontour. There as no systolic pressure gradient across the aortic valve. Biplane ascending aortogra ph disclosed the following: there was minimal refl of contrast material i to the left ventricle (Fig. 4), indicat ng minimal aortic insufficiency the aortic l as seen in both projections had t cusps divided by single commissure which lay in the sagittal plane (Figs. 4 and 5). I the posteroanterior projection the aortic ar h nd upper descending aorta had t apparent on tractions the proximal *part of the left subcla ia artery was dilated and* kinking of the vessel was evident (Fig. 6). At the distal arch the aorta narrowed t about half the aliber of the rest of the aorta doubled forward on tself then looped backward nd idened to continue downward as the descending aorta this as best seen the lateral projection (Fig. 7). The left erte-bral artery as distinctly smaller than the right (Fig. 6) nd opacified about one half second after the right. *The right subcla ian artery* beyond its first part opacified little and late, presumably because of hyperabduction of the right arm t the time and pressure on the brachial artery during the injection of contrast material.

Discussion

Pseudocoarctation of the aorta is re garded as a rare congenital anomaly n It has been observed as early as 10 years of age [7] A variety of congenital defects of the heart and aorta have been associated with this anomaly These include ventricular septal defect [4] corrected transposition of



Fig. 3 Chest roentgenogram in marked left anterior oblique projection (near-lateral). Note the pronounced notch posteriorly near the upper end of the aortic shadow. Further described in text.





Figs. 4 and 5 Ascending aortogram, posteroanterior (*top*) and lateral (*bottom*) projections, at one and two-thirds seconds after injection. Two aortic valve cusps are seen, divided by a single commissure. Further described in text.

the great vessels with dextrorotation of the heart, aneurysm of the sinus of Valsalva,[8] and aortic valvular stenosis. The occurrence of mild coarctation (pseudocoarctation) and true coarctation of the aorta has been reported in brothers.[22]

Steinberg[17] described 4 patients with associated aortic valvular stenosis; two of his patients were subsequently proved to have a bicuspid aortic valve, at operation in one and at autopsy in the other. Our patient appears to be the first in whom an associated bicuspid aortic valve was diagnosed radiographically. The incidence of bicuspid aortic valve in this condition could be considerable, as in the case of true coarctation, but the roentgenographic techniques necessary to reveal it have been infrequently employed. The importance of this observation is obvious since the incidence of subacute bacterial endocarditis on a bicuspid aortic valve is high and significant aortic valvular stenosis or insufficiency may also develop in the course of time.[23] Although the presence of a bicuspid aortic valve can be suspected clinically on the





Figs. 6 and 7. Ascending aortogram posterior anterior (top) and lateral (bottom) projections, at two and one-third seconds after injection. The shadow of the small left vertebral artery is superimposed on that of the left common carotid artery. Note the pronounced kink of the left subclavian artery proximal to the origin of the vertebral artery. Further described in text.

basis of murmurs biplane ascending aortography by means of retrograde catheterization of the right brachial artery would appear to be the method of choice for demonstrating the anatomy of the aortic valve as well as that of the thoracic aorta in cases such as the present one. Pseudocoarctation can also mimic mediastinal tumor aneurysm of the aortic arch or true coarctation lesions which carry entirely different implications of therapy and prognosis. Some patients with pseudocoarctation have been subjected to exploratory thoractomy or radiotherapy for mediastinal tumor.[11,14]

The pathogenesis of pseudocoarctation has been attributed to failure of compression of the left fourth aortic arch and certain segments of the dorsal aortic root.[12] This is presumed to result in buckling of the aortic arch between two fixed points the aortic valve ring and the attachment of the ligamentum arteriosum. Consequently the summit of the aortic arch rises to an abnormally high position. Elongation and dilatation of the left subclavian artery may be associated with pseudocoarctation. Superimposed progressive enlargement of the vascular shadow in this region as was reported by Soma may be engendered by hypertension or arteriosclerosis or both in the older patient. These various factors easily account for the kinking of the proximal left subclavian artery noted in the present case. In turn obstruction at this strategic location may cause reversal of blood flow in the ipsilateral vertebral artery which then drains into the more distal subclavian artery.

The syndrome of subclavian steal,[16] suspected in the present case, was first described by Contorni[17] and Reivich and associates[18] and has since been extensively studied.[19-23] Arteriosclerotic plaque formation in the proximal subclavian artery is the common cause of the obstruction which results in reversal of flow in the vertebral artery. The syndrome may also occur after Blalock Taussig anastomosis. Proximal subclavian artery obstruction and brachial vertebral arterial flow demonstrated angiographically are the important diagnostic criteria. However reversed vertebral arterial flow need not be large in amount nor occur steadily since its degree is deter

mined principally by the degree of obstruction of the ipsilateral subclavian artery, the existing collateral circulation, and the metabolic needs of the involved extremity at the particular time. Sammartino and Toole[41] have shown experimentally in the dog that such reversal of flow after acute occlusion of the right subclavian artery varied in volume with the systemic blood pressure and increased during exercise of the right forelimb. Left subclavian steal was suspected in this patient because of the clinical history and evidence of obstruction of the left subclavian artery, notably a relatively weak left brachial pulse (not described as a feature of pseudocoarctation) and a vascular bruit over the region of the proximal left subclavian artery. This was not confirmed angiographically under the conditions of the test. However, kinking of the left subclavian artery proximal to the vertebral artery was found and is the presumed cause of partial obstruction of that vessel. If the setting in which this kinking has occurred is taken into account, its progression to a lesion of greater hemodynamic and clinical importance is a reasonable possibility.

This case serves to emphasize the association of bicuspid aortic valve with pseudocoarctation. It also illustrates that pseudocoarction may have mechanical effects which in this instance caused or predisposed to buckling of the proximal left subclavian artery with resulting partial obstruction and some evidence of subclavian steal which was not, however, of clear-cut clinical importance at the time of the studies.

Summary

This case report concerns a 50-year-old woman with clinical features suggestive of left subclavian steal. In addition to a bicuspid aortic valve, pseudocoarctation of the aorta and a kinking of the proximal left subclavian artery were demonstrated angiographically. The association of kinked left subclavian artery with pseudocoarctation has not been reported previously. The possible basis of this association is discussed, as is the relationship between the kinked subclavian artery and the clinical evidence of subclavian steal. Although subclavian steal was not proved angiographically the conclusion is that the setting favors its hemodynamic and clinical progression.

We are indebted to Dr. M. M. DiGilio for permission to study and report his case. We are also indebted to Dr. L. N. Katz for his advice in the preparation of this report.

REFERENCES

1. Souders, C. R., Pearson, C. M., and Adams, H. D.: Aortic deformity simulating mediastinal tumor: Subclinical form of coarctation, Dis. Chest 20:35, 1951.
2. Dotter, C. T., and Steinberg, I.: Angiocardiography, New York, 1951, Paul B. Hoeber, Inc., p. 181.
3. Robb, G. P.: Atlas of angiocardiography. Prepared for American Registry of Pathology, A. F. I. P., National Research Council, Washington, D. C., 1951.
4. Steinberg, I.: Anomalies (pseudocoarctation) of the arch of the aorta, Am. J. Roentgenol. 88: 3, 1962.
5. Dotter, C. T., and Steinberg, I.: Angiocardiography in congenital heart disease, Am. J. Med. 12:219, 1952.
6. Di Guglielmo, L., and Guttadauro, M.: Kinking of aorta, Acta Radiol. 44:121, 1955.
7. Bruwer, A. J., and Burchell, H. B.: Kinking of aortic arch (pseudocoarctation, subclinical coarctation), J. A. M. A. 162:1445, 1956.
8. Steinberg, I.: Aneurysm of aortic sinuses with pseudocoarctation, Brit. Heart J. 18:85, 1956.
9. Wigham, B. F.: Kinking of aortic arch, Brit. J. Radiol. 29:516, 1956.
10. Bruwer, A. J.: Kinking of aortic arch simulating mediastinal tumor, Brit. J. Radiol. 30:387, 1957.
11. Stevens, G. M.: Buckling of aortic arch (pseudocoarctation, kinking): roentgenographic entity, Radiology 70:67, 1958.
12. Pattinson, J. N., and Grainger, R. G.: Congenital kinking of aortic arch, Brit. Heart J. 21:555, 1959.
13. Ross, P.: Kinking of the aortic arch, Med. J. Australia 6:864, 1959.
14. Godbjerg, C. E., and Petersen, O.: Coarctation of aorta: Relation between roentgenologic and hemodynamic findings, Radiology 75:399, 1960.
15. Sarle, S., Vletic, V., Gvozdanovic, V., and Mark, B.: A case of kink of the aortic arch, Circulation 21:1147, 1960.
16. Barrett, A. F., and Verney, G. I.: Kinking of aortic arch associated with fusiform aneurysmal dilatation, Clin. Radiol. 11:100, 1960.
17. Steinberg, I., and Hagstrom, J. W. C.: Congenital aortic valvular stenosis and pseudocoarctation ("kinking, buckling") of arch of aorta: Report of four cases including autopsy study of one case with parietal endocardial fibrosis and fibroelastosis, Circulation 25:545, 1962.
18. Edmunds, L. H., Jr., McClenathan, J. E., and Hufnagel, C. A.: Subclinical coarctation of the aorta, Ann. Surg. 156:180, 1962.
19. Griener, J. T., and Weisburg, R. J.: Pseudo-

coarctation of the aorta, Minnesota Med. 46 128 1963
20 Fowell, J W Abnormal mediastinal shadow n chest film New Physician 12:427 1963
21 Berry R. E. Griffith J R. and Templeton, J Y Kinking of orta Am Surg 29:65 1963.
22 Klein M M and Walsh E L Kinking nd buckling of the thoracic orta sim lating mediastinal tumors, Souther M J 57 171 1964
23 Griffin, J F Congenital kinking of the aorta (pseudocoarctation) New England J Med 271 726 1964
24 Soma F D and T igg H L Kinking of the thoracic orta, Gen. Pract 24 126 1964
25 Keller H I nd Chettlin M D The occurrence of mild coarctation of the aorta (pseudocoarctation) and coarctation one family Am Heart J 70 113 1965.
26 Beck, J L Roentgenogram of the mouth Dis Chest 47:649 1965
27 Steinberg, I Pseudocoarctation of aorta, Med. Sc 16 7 1965.
28 Ed rds, J E. (Editorial' Congenital bicuspid ortic valve, Circulation 23:485, 1961
29 Poker N Finby N and Steinberg I The subclavia arteries Roentgen study in health and disease Am J Roentgenol 80 193, 1958.
30. Editorial A new vascular syndrome 'The subclavian steal, New England J Med 265:912 1961
31 Contorni, L Il circolo collaterale vertebrovertebrale nella obliterazione dell arteria suc cla la alla ne origine, Minerva Chir 15:268 1960.
32 Reivich, M Holling H. E Roberts, B nd Toole J F Reversal of blood flow through the ertebral artery and its effect on cerebral circulation New England J Med 265:878, 1961
33 North, R. R., Fields, W S DeBakey M E. and Crawford, E. S Brachial-basilar insuf ficiency yndrome Neurology 12:810, 1962
34. Samon, M Rabinov K and Horenstein, S Proximal subclavia artery occlusion and reversed vertebral blood flow t the arm, Clin Radiol. 13:201 1962
35. Philip, T Samuel, E and Duncan, J G. Reversed vertebral artery blood flow in subclavian artery obstruction (subclavian steal) Clin. Radiol. 14:310, 1963.
36. Williams, C. L., Scott, S. M and Takaro, T Subclavian steal, Circulation 28 14 1963.
37 Fischer M J and Matt y W E The subcla ia teal yndrome Am J Roentgenol 90:532, 1963.
38 Ashby R N Karras, B G., and Cannon, A H Clinical and roentgenographic aspects of the subclavian teal syndrome Am J Roentgenol. 90:535 1963
39 Steinberg, I and Halpern, M Roentgen ma ifestation of the subclavian teal yndrome Am J Roentgenol. 90:528, 1963.
40. Callow A D Surgical management of varying patterns of vertebral artery and between artery insufficiency New England J Med. 270:546 1964
41 Pollner P The subclavian steal syndrome, Chicago Med. Sch Quart 24:36, 1964
42 Sammartino, W F and Toole, J F Reversed vertebral artery flow The effect of limb exercise nd hypertensive agents, Arch. Neurol 10:590, 1964.
43 Conrad, M Toole, J Janeway R and Green, H Acute and chronic effects of arterial occlusion on vascular hemodynamics, Fed Proc 23:207 1964.
44 Toole J F (Editorial) Reversed vertebral flow nd cerebral vasc lar insufficiency An Int. Med 61 159 1964
45 Cameron, D J nd Wright I S Subclavian steal yndrome with olfactory hallucinations, Ann I t Med 61:64 1964
46 Heyman A Young W G Jr Dillon, M Goree I A. Klein, L J and Tindall, G Cerebral ischemia caused by occlusive lesion of subclavian or nominat arteries, Arch Neurol. 10:581 1964.
47 Curry J L and Howland, W J Subclavian teal yndrome. Pitfalls i it diagnosis, Am. J Roentgenol 91 1254 1964.
48 Newton T H and Wylie, E. J Collateral circulation associated with occlusion of the proximal subclavian or innominat arteries, Am. J Roentgenol. 91:394, 1964
49 Ethier R. Observation on retrograde vertebral artery blood flow Am J Roentgenol 91 1243 1964
50 Shockm A T Retrograde ertebr l flow as an artifact of tech ique Am. J Roentgenol. 91 1258, 1964
51 Foger G M and Shah K D Subclavian steal i patients with Blalock Taussig anastomosis, Circulation 31:241 1965.
52 Marshall R. J and M tinl, E. L. Dynamics of the collateral circulation in patients with subclavia steal Circulation 31:249 1965.
53 P tel, A and Toole J F Subclavia steal yndrome—Reversal of cephalic blood flow Medicine (Baltimore) 44:289 1965.

Removal of an iatrogenic foreign body from the aorta by means of a ureteric stone catcher

B W Lassers M.B Ch.B
D Pickering M.B B S D C.H
Edinburgh Scotland

Iatrogenic foreign bodies in the heart and great vessels are an uncommon but well-recognized complication of cardiac catheterization. Usually the removal of such objects has been regarded as being advisable and the majority have been retrieved by direct operation on the chamber of the heart or the great vessel in which the object was situated. This of necessity entails a major operative procedure involving thoracotomy or intra abdominal surgery. The following case report describes the removal of such a foreign body from the descending aorta by retrograde catheterization via the femoral artery employing a catheter originally designed to remove stones from the ureter.

Case report

The patient was a 43-year-old woman with advanced rheumatic heart disease involving both the aortic and the mitral valves. Left heart catheterization was carried out by the Brockenbrough transseptal technique as part of assessment for operative treatment. During this procedure difficulty was encountered in maneuvering the catheter from the left atrium through the mitral valve into the left ventricle. A stainless-steel spring-tipped guide wire which had been examined for faults prior to use was then passed through the catheter in an attempt to facilitate this passage. The guide wire was advanced beyond the end of the catheter and after several attempts had been made to negotiate the valve in this manner the spring-tip comprising the distal 3 cm. of the guide wire broke off and remained in the left atrium. The procedure was abandoned at this stage and it was decided to proceed directly to thoracotomy in order to remove the wire.

Immediately prior to operation, which was performed 3 hours later, a roentgenogram was taken which showed the wire to be lying either low in the left atrium or just below the mitral valve (Fig 1). At operation, however, the wire could not be located in either the left atrium or the left ventricle. A valvulotomy was carried out on a tightly stenosed mitral valve. Postoperative roentgenograms showed the wire to be in the descending aorta at the level of the eleventh thoracic vertebra (Fig 2). No further attempt at removal was made. Postoperatively the patient was started on anticoagulant treatment and made an uneventful recovery from the valvulotomy. Roentgenograms taken during convalescence showed that the wire had not moved.

The decision was made to remove the wire under general anesthesia and fluoroscopic control, employing a Dormia ureteric stone catcher† passed through a right femoral arteriotomy. This flexible instrument consists of an outer nylon catheter enclosing a movable metal wire the distal end of which consists of a collapsible wire basket (Fig 3). By controlling the wire from its proximal end and advancing it up the catheter about 5 cm the basket slides out of the distal end and opens. By drawing the wire back, the basket slides back into the catheter and closes (Fig 4).

The stone catcher was advanced up the aorta

From the Department of Cardiology, Royal Infirmary, Edinburgh, and the Cardiological Unit, Western General Hospital, Edinburgh, Scotland.

Received for publication May 16, 1966.

Registrar, Department of Cardiology, Royal Infirmary. Address: Department of Cardiology, Royal Infirmary, Lauriston Place, Edinburgh 3, Scotland.
**Registrar, Cardiological Unit, Western General Hospital.

†Manufactured by Endoscopic Instrument Co., London, England.



Fig. 1. Pre-thoracotomy roentgenograms showing the tip of the guide wire in the left atrium.

Fig. 2. Lateral roentgenogram taken after thoracotomy showing the tip of the guide wire in the descending aorta opposite T

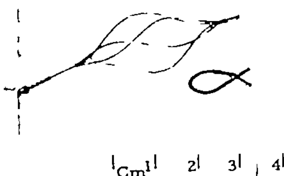


Fig. 3. Photograph showing the distal end of the stone catcher in the open position with the tip of the flexible guide wire below.

until its tip lay above the broken wire and the basket was then opened. After some maneuvering the wire was engaged by the basket, which was then closed. The catheter with the tip of the wire was then withdrawn down the aorta and through the arteriotomy (Fig. 5). In order to prevent the wire from entering the left femoral artery should it have been knocked free during the procedure the vessel was occluded by means of a sphygmomanometer cuff around the left thigh. After the wire had been removed, the patient made an uneventful recovery and was discharged home 4 days later.

Discussion

Indications for removing foreign bodies. It has been generally assumed that foreign bodies within the heart and great vessels should be removed because of (1) the danger of thrombus formation and subsequent embolization, (2) the possibility of perforation of the heart or vessel with hemorrhage or hemopericardium, (3) the danger of embolization of the foreign body itself, (4) the risk of infection.

Although foreign bodies have been described as being in the heart for periods of over 20 years without complications,[3] peripheral embolization including cerebral embolization with hemiplegia has been recorded. Furthermore clot has often been noted on foreign bodies removed from the heart or vessels, and almost certainly an increased risk of embolic complications exists in these cases.

The presence of intracardiac foreign bodies also produces a risk of myocardial perforation with *hemopericardium* and tamponade. This has been reported particularly with polyethylene cannulas and pacemaker catheters.[4] In the case of arteries or veins, the situation is somewhat different since it is probably myocardial contraction itself which forces the object through the heart wall. Cope[4] has reported an instance of a guide wire tip being left in the iliac vein for 1 year without further difficulties.

Embolization of the foreign body itself

may also occur. Scebat and associates de scribed the embolization of a polyethylene cannula from the right side of the heart into the pulmonary artery without further com plications, but Knutson and Stenberg[3] reported fatal pulmonary embolism from such an event. Thoracotomy was carried out in our case because it was thought that em bolization, particularly cerebral emboliza tion, was a definite danger. The wire did in fact, embolize and it is perhaps only fortuitous that it passed into the descend ing aorta rather than into the cerebral circulation. Further movement of the wire distally was not regarded as being a serious danger since it could then have been removed by simple arteriotomy.

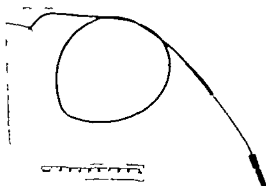


Fig. 4 Photograph showing the stone catcher in the losed position with the fragment of guide wire engaged.

The risk of infection introduced with a foreign body would appear also to be of importance. Taylor and Rutherford[9] men tion five deaths due to infected polyethy lene Intracaths which had embolized from a peripheral vein. Harken and Zoll re ferred to experimental work on dogs in which foreign bodies introduced into the heart resulted in the spontaneous develop ment of subacute bacterial endocarditis, but they had no unequivocal evidence that this occurred in their clinical series.

In summary, although foreign bodies may be left in the heart or great vessels for long periods without serious complications aris ing, the risk of thrombus formation with subsequent embolization, of myocardial perforation, of embolization of the object itself, and of the development of infection is sufficiently great to warrant the removal of all such objects whenever possible.

Use of the ureteric stone catcher. Our use of the ureteric stone catcher in this case was prompted by the location of the wire at a site to which surgical access would have been difficult and by the desire to avoid a second major surgical procedure. For simi lar reasons, Thomas and associates[1] em ployed bronchoscope biopsy forceps intro duced through the saphenous vein to re move the tip of a guide wire from the right atrium and inferior vena cava. These authors commented that this rigid instru ment was not ideal for this purpose because of the possibility of perforation of the vena

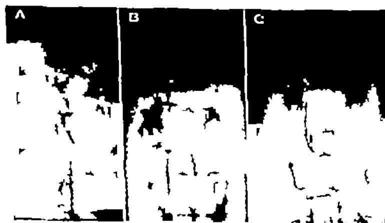


Fig. 5 Photograph of frames from cine film taken during withdra l of the tip of the guide wire, showing it t the level of (A) T_{12}, (B) the upper border of L_4, and (C) the upper border of L

cava. They added that there was an obvious need for a flexible instrument for retrieval of such foreign bodies.

There is certainly a similar if not greater danger in using such a rigid instrument in the aorta. This disadvantage is not present with the stone catcher which could therefore be used for removal of foreign bodies from either the right atrium or the aorta. In our case the procedure was easily and quickly performed with minimal risk to the patient. Although general anesthesia was employed the procedure could probably have been done with local anesthesia alone.

The use of the stone catcher for the retrieval of intravascular foreign bodies has obvious limitations. It would be impossible to remove objects from the left ventricle by this technique, and the left atrium is also inaccessible. Furthermore if the foreign body is sharp or unduly rigid there is a danger of damage to the vessel wall during withdrawal. In the case of the wire tip which is very flexible (Fig. 3) this danger is slight.

Despite these limitations and the fortunately infrequent necessity for employing such an instrument it is thought that the ureteric stone catcher may have a valuable role to play in the retrieval of iatrogenic foreign bodies.

Summary

A case is presented in which the tip of a guide wire that was lost in the left atrium during Brockenbrough transseptal catheterization and subsequently embolized to the descending aorta was retrieved by retrograde catheterization employing a catheter originally designed for removal of stones from the ureter. The indications for removal of intravascular foreign bodies and the use and limitations of the stone catcher for this purpose are discussed.

We wish to thank Dr. R. M. Marquis and M. A. Logan for their assistance and permission to publish this case, and M. W. Selby Tulloch for use of the instrument.

REFERENCES

1. Lillehei, C. W., Bonnabeau, R. C., and Grow-long, S.: Removal of iatrogenic foreign bodies within cardiac chambers and great vessels, Circulation 33:782, 1965.
2. Decker, H. R.: Foreign bodies in the heart and pericardium—Should they be removed? J. Thoracic Surg. 9:62, 1940.
3. Harken, D. E., and Zoll, P. M.: Foreign bodies in and in relation to the thoracic blood vessels and heart, AM. HEART J. 32:1, 1946.
4. T[illegible]gan, H., and Dudotte, J.: Prolonged survival after catheter embolism, Ann. Int. Med. 58:564, 1963.
5. N[illegible]than, A., Center, S., Pina, R. E., Medow, A., and Keller, W.: Perforation during indwelling catheter pacing, Circulation 33:128, 1966.
6. Cope, C.: Intravascular breakage of Seldinger spring guide wires, J.A.M.A. 180:1061, 1962.
7. Scebat, L., Renais, J., Meeus-Bithe, L., and Lenegre, J.: Accidents, indications et contre-indications du cathétérisme des cavités droites du coeur, Arch. Mal. Coeur 50:943, 195[illegible]
8. Knutson, H., and Stenberg, K.: Pulmonary embolus with foreign body, Nord. Med. 62:1491, 1959.
9. Taylor, F., and Rutherford, C.: Accidental loss of plastic tube in the venous system, Arch. Surg. 86:177, 1963.
10. Thomas, J., Sinclair-Smith, B., Bloomfield, D., and Davachi, A.: Non-surgical retrieval of broken segment of steel spring guide from the right atrium and inferior vena cava, Circulation 30:106, 1964.

Review

Calcium exchange in cardiac muscle: A basic mechanism of drug action

Winifred G. Nayler, D.Sc.
Victoria, Australia

"The action of the organ is so plainly contraction its function is to propel blood into the arteries."
Harvey,[1] *De Motu Cordis*, 1628

In 1616, twelve years before the publication of *Exercitatio Anatomica de Motu Cordis et Sanguinis*, Harvey wrote "the movement of the blood is constantly in a circle, and is brought about by the beat of the heart,"[2] from which it can be concluded that he then understood and appreciated that *contraction* was an important function of the heart. Two hundred and fifty years elapsed before Ringer[3] demonstrated that the maintenance of the heart's ability to contract and hence to *propel* blood into the arteries depended upon the continuing but regulated availability of calcium ions, Ca^{++}. Interest in the mechanisms which regulate the intracellular distribution and concentration of Ca^{++} in muscle cells, and which by so doing facilitate either contraction or relaxation, has steadily increased since 1947 when Heilbrunn and Wiercinski[4] first demonstrated that an intracellular injection of Ca^{++} but not Mg^{++} initiated contraction. Precisely how Ca^{++} activate contraction, that is, the interaction between the thin actin and thick myosin filaments shown schematically in Fig. 1, is not known,[5] but many investigators, including Ebashi,[6] Weber and Herz,[11] and Weber and Winicur[12] have shown that it is the concentration of Ca^{++} which determines whether, in the presence of adenosine triphosphate (ATP), the actomyosin complex remains relaxed or contracted. This review has been prepared as an attempt to correlate the available data relative to the mechanisms whereby the concentration of Ca^{++} in cardiac muscle cells is adjusted to promote either contraction or relaxation, and to explore the possibility that the system which regulates this intracellular concentration of Ca^{++} represents a primary site of action for certain cardioactive drugs. Readers are referred to an earlier review[4] for a detailed description of the cellular structure of cardiac muscle and to the recent review by Sandow[5] for further information relative to the events which probably are involved in excitation-contraction coupling in skeletal muscle.

Excitation-contraction coupling and Ca^{++}

The membranes of quiescent cardiac muscle cells resemble those of quiescent skeletal and smooth muscle in that they are electrically polarized,[13] the inside of each cell being negative with respect to

From the Baker Medical Research Institute, Victoria, Australia.
This review was prepared during the tenure of grant-in-aid from the National Heart Foundation of Australia.
Received for publication Sept. 6, 1966.
Address: Baker Medical Research Institute, Commercial Road, Prahran S 1, Victoria, Australia.

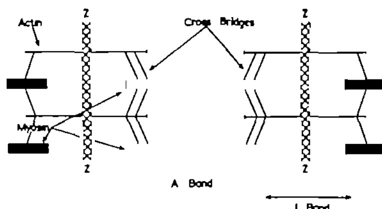


Fig. 1. Schematic representation of the relationship between the contractile proteins, actin and myosin and the cross-bridges.

the outside. Excitation which precedes and triggers off the series of events which culminate in contraction[1-4] occurs when the transmembrane potential difference is abolished or reversed and involves a change in the selective permeability of the excited cell membranes to certain ions, including Na^+, K^+ and Ca^{++}.[17,21] That the link between membrane depolarization and contraction (*excitation-contraction coupling*) requires the presence of extracellular Ca^{++} is already well documented.[22] As early as 1907 Locke and Rosenheim[8] reported that, if Ca^{++} are removed from solutions bathing isolated cardiac muscle preparations, the spontaneous action currents remain long after the mechanical beat has become minimal. Sr^{++} and Ba^{++} can replace Ca^{++} in establishing the link between excitation and contraction in both cardiac and skeletal muscle but, since neither Ba^{++} nor Sr^{++} is available under in vivo conditions, the physiologic significance of this substitution is limited.[23,24]

The experiments of Niedergerke,[24] Podolsky and Constantin,[25] and Heilbrunn and Wiercinski showed that the contractile mechanism can be activated simply by increasing the intracellular concentration of Ca^{++}. They failed, however, to provide any indication of the critical concentration of Ca^{++} which is required to effect this activation. Using a suitably buffered Ca solution Portzehl, Caldwell, and Rüegg[26] were able to demonstrate that activation of the contractile mechanism occurred in previously relaxed cannulated single muscle fibers when an intracellular concentration of 0.3-1.4 μM Ca^{++} was established. Their observations related to skeletal muscle only, and comparable quantitative data have not yet been obtained for cardiac muscle, but, since there is no valid reason to suspect that the actomyosin ATP system in cardiac muscle differs from that in skeletal muscle with regard to its sensitivity to Ca^{++}, we can assume that approximately this same concentration of Ca^{++} would activate the contractile mechanism in cardiac muscle cells. Since excitation-contraction coupling fails in the absence of extracellular Ca^{++}[4,20] and since an intracellular accumulation of Ca^{++} can, under certain conditions, activate contraction, the question arises whether excitation or some process associated with excitation facilitates an inward movement of Ca from the extracellular fluid into the cell, thereby providing an intracellular concentration of Ca^{++} which is high enough to activate contraction.

Uptake of Ca^{++} (as Ca^{45}) by quiescent and stimulated cardiac muscle

When quiescent cardiac muscle is immersed in an aerated physiologic saline solution containing Ca^{45}, it resembles skeletal muscle[27] in that it accumulates Ca^{45}. Grossman and Furchgott[28] found that quiescent guinea pig atria immersed for 5 minutes in Ca^{45}-labeled Krebs solution containing 2.32 mM Ca^{++} accumulated 0.50±0.04 mM Ca^{45} per kilogram wet weight, compared with 0.22±0.04 mM Ca^{45}/Kg. wet wt. when the Ca^{++} in the

Table I Uptake of Ca^{45} by quiescent cardiac muscle in relationship to extracellular Ca^{++} and Na^{+}

Preparation	Extracellular concentration		Uptake of Ca^{45} (μμ mole/cm²/sec.)
	Ca^{++} (mM)	Na^{+} (mM)	
Guinea pig atria[16]			
	1 25	145	0 016 ± 0 003
	2 50	145	0 029 ± 0 001
	3 75	145	0 048 ± 0 009
Frog ventricle[38]			
	1 0	116	0 009
	1 0	58 + sucrose	0 11

Krebs solution was reduced to 1 09 mM Niedergerke[38] detected an uptake of 0 009 μμ mole Ca^{45} per square centimeter per second in quiescent frog ventricular muscle immersed in Ca^{45}-labeled Ringer solution containing 1 mM Ca^{++} and Nayler[39] described an uptake of 0 024±0.003 μμ mole Ca^{45}/cm²/sec. by quiescent toad ventricular muscle immersed in Ca^{45} labeled Ringer solution containing 1.3 mM Ca^{++}

The uptake of Ca^{++} by quiescent cardiac muscle is proportional to the extracellular concentration of Ca^{++} and inversely proportional to that of Na^{+} as is shown by the data listed in Table I Conditions which stimulate the uptake of Ca^{++} in *quiescent* cardiac muscle are identical therefore with those which when applied to actively contracting preparations, result in augmented contractions.[38,41-43] The question arises, then whether the uptake of Ca^{++} in actively contracting cardiac muscle differs significantly from that in resting preparations

Many investigators, including Winegrad and Shanes, Niedergerke[38] Langer[44] and Grossman and Furchgott,[38] have shown that in cardiac muscle as in skeletal muscle[17] contraction is accompanied by an increase in the uptake of Ca^{++} relative to that found in resting preparations. In frog ventricular muscle immersed in 1 mM Ca^{++} Ringer solution and stimulated to contract ten times per minute there is, for example superimposed upon the resting uptake of Ca^{++} of 0 009 μμ mole Ca^{45}/cm²/sec an additional uptake of 0.15 μμ mole Ca^{45}/cm²/beat.[38] Dog papillary muscles immersed in a physiologic saline solution containing 3 mM Ca^{++} take up as much as 0 92 μμ mole Ca^{45}/cm²/beat[4] in addition to the resting uptake of Ca^{++} Other data which relate to the uptake of Ca^{++} by actively contracting cardiac muscle are listed in Table II and show that the magnitude of the influx of Ca^{++} per beat is related both to the frequency with which contraction occurs and to the extracellular concentrations of Na^{+} and Ca^{++} These data indicate, therefore that conditions which favor the uptake of Ca^{++} in *actively contracting* cardiac preparations are identical with those which enhance contractions.[4,37]

Electrical stimulation represents only one of the methods available for abolishing or reversing the transmembrane resting potential. In accordance with the ionic basis of electrical activity in muscle cells[21] this transmembrane resting potential is reduced and then *reversed as the extra*cellular concentration of K^{+} is raised Niedergerke[38] and others have shown that the magnitude of the contracture which develops in cardiac muscle when it is immersed in a K^{+}-enriched Ringer solution containing Ca^{++} is markedly dependent upon *the available extracellular Ca* Such K^{+} induced contractures are associated with an augmented uptake of Ca thus according to Niedergerke's data[38] frog ventricular muscle which is immersed in 100 mM K 1 mM Ca^{++} Ringer solu

Table II Uptake of Ca^{45} by actively contracting cardiac muscle in relationship to extracellular Ca^{++} Na^{+} and frequency of contraction

Preparation	*Extracellular concentration*		*Stimulation rat (per min)*	*Additional influx (μμ mole Ca^{45}/cm /beat)*
	Ca^{++} (mM)	N (mM)		
Guinea pig atria[1]				
Series A	2 5	145	30	0 55 ± 0 14
	2 5	145	6	0 15 ± 0 043
Series B	1 25	145	15	0 13 ± 0 003
	2 50	145	15	0 30 ± 0 055
	3 75	145	15	0 44 ± 0 042
Frog ventricle[4]				
	1	116	10	0 15
	2	116	10	0 23
	0 5	58+ sucrose	10	0 27

tion takes up as much as 0 11 μμ mole Ca^{45} cm sec that is, more than ten times the amount of Ca^{++} (0 009 μμ mole Ca^{45} cm sec) which is taken up by quiescent ventricular muscle immersed in ordinary 1 mM Ca^{++} Ringer solution This influx of Ca^{++} into muscles which are bathed with K^{+}-enriched Ringer solution becomes even more marked as the concentration of Na in Ringer solution is reduced [33]

Calcium influx and activation of contraction

Because the contractile mechanism in a particular cell can be activated by increasing the intracellular concentration of Ca^{++} and because contraction in cardiac muscle is associated with an enhanced influx of Ca^{++} the question arises whether during normal excitation-contraction coupling those particular Ca^{++} which enter the cell during the period of increased influx of Ca directly activate contraction causing the thin actin filaments to slide between the thick myosin filaments [7,43] Alternatively the Ca^{++} which participate in the increased influx associated with excitation may trigger off the release of Ca^{++} from intracellular Ca storage sites and these released ions then activate the contractile mechanism Recently Sandow[4,14] considered this problem in relation to skeletal muscle and concluded that although excitation of skeletal muscle i undoubtedly accompanied by an enhanced uptake of Ca^{++} the presently available data relating to Ca flux studies fail to substantiate the theory that contraction in skeletal muscle is activated by those particular Ca^{++} which enter the muscle in association with or as a direct result of the excitation-induced depolarization He concluded however that an internal release and translocation of ionized Ca almost certainly provides the basis for activation of contraction in skeletal muscle the Ca^{++} being released from the Ca loaded membranous sacs,[11] the lateral cisternae of the triads,[49] possibly in response to the increased influx of Ca^{++} associated with the excitatory stimulus These lateral cisternae are a specialized part of the sarcoplasmic reticulum and in skeletal muscle lie in close proximity to the transverse tubules (the 'T' system) which communicate directly with the extracellular space [41] and which probably represent a direct extension or continuation of the plasma membrane within the sarcoplasm [43] Winegrad s autoradiographic studies[43] [1] substantiate the hypothesis that in skeletal muscle contraction is accompanied by or associated with a translocation of intracellularly stored Ca^{++} In cardiac muscle however the studies of Ca^{45} of Niedergerke[37] and Winegrad indicate that activation of contraction *could directly involve* and depend upon these Ca^{++} which enter the muscle during or as the im

mediate result of excitation. Data already referred to in Table II indicate that the magnitude of this influx of Ca^{++} is determined by the frequency with which contraction is initiated and by the extracellular concentration of Ca^{++} and Na^{+}. If the contractile mechanism in cardiac muscle is activated by those Ca^{++} which enter the cells during excitation, then the magnitude of each contraction should, as it does, reflect the duration of the interval which separates it from its predecessor (as in the staircase and other frequency-dependent phenomena[17,44]) and the extracellular concentrations of Ca^{++} and Na^{+}. The experiments of Lüttgau and Niedergerke[17] and Wilbrandt and Koller[43] have shown that this last proposition is true.

According to Niedergerke's data, several phases of Ca^{++} exchange occur in the interval between the initial excitation-induced increase in the influx of Ca^{++} and the onset of contraction in cardiac muscle, so that only part of the total exchangeable Ca^{++} may be involved in promoting contraction. Using actively contracting arterially perfused dog papillary muscles, Langer[4] investigated this problem and concluded that, of the five kinetically defined phases of Ca^{++} exchange which he could detect, the maintenance of myocardial contractility resided almost exclusively in that fraction which represented itself in his system as Phase 2 and which had a time constant of 8.62 minutes. Langer suggested that this kinetically identifiable Phase 2 may be predominantly representative of Ca^{++} in the sarcoplasmic reticulum," but the additional evidence needed to substantiate this speculation is not yet available.

Those particular Ca^{++} which activate contraction in cardiac muscle may, as Niedergerke has suggested,[19,34] initially combine with a superficially located cellular membrane and then, by forming a soluble complex, move across the membrane to be released into the myoplasm in the vicinity of the myofibrils, as activator Ca. Such a system is shown schematically in Fig. 2, where it is compared with that already described for skeletal muscle. This comparison gives emphasis to a fundamental difference which probably exists between Ca^{++}-induced excitation-contraction coupling in cardiac muscle and that in skeletal muscle. In skeletal muscle the increase in the intracellular concentration of Ca^{++} which results directly from the augmented influx of Ca^{++} associated with excitation serves as a

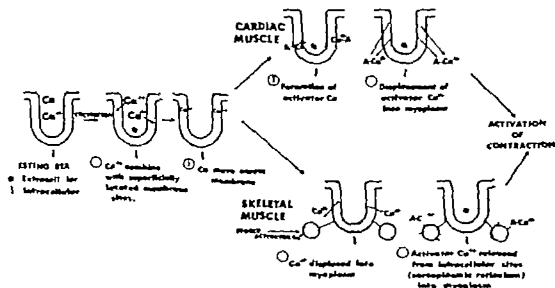


Fig. 2. Diagrammatic representation of the events involved in excitation-contraction coupling i cardiac nd sk letal muscle. Note the difference in the site of formation of activator-calcium, *A Ca++*

trigger to release activator-Ca from secondary stores within the muscle whereas in cardiac muscle activator-Ca is formed by the combination of extracellular Ca^{++} with that at superficially located sites in cell membranes and the activator-Ca so formed is displaced into the myoplasm during excitation. The release of activator-Ca from the triad in skeletal muscle resembles to some extent the release of catecholamines from intracellular storage granules; it is a Ca^{++}-dependent phenomenon and may represent another example of the involvement of ionized Ca^{++} in stimulus-secretion coupling as discussed by Douglas and Rubin. This difference between the origin and location of activator-Ca in skeletal and cardiac muscle may be responsible for some of the differences which are apparent in the reactions of these muscles to common stimuli. Thus although excitation-contraction coupling fails in skeletal and cardiac muscle alike if extracellular Ca^{++} are absent, the addition of other divalent cations including Zn^{++}, Co^{++}, Ni^{++}, and Be^{++} restores this link between excitation and contraction in skeletal muscle but not in cardiac muscle. The ability of these other divalent cations to replace Ca^{++} in skeletal muscle but not in cardiac muscle probably is due to their ability to displace activator-Ca from the specialized stores of endogenous Ca present in skeletal muscle. The cyclic and excitation-dependent formation of "activator-Ca" in cardiac muscle may have its purpose in preventing the possible onset of prolonged periods of contraction which would interfere with the primary function of the heart, that is, the propulsion of blood into the arteries. In skeletal muscle, however, the prolonged release of activator-Ca from intracellular storage sites may facilitate the maintenance of sustained contraction for prolonged periods.

Ca^{++} and relaxation

If ionized Ca^{++} is the mediator in excitation-contraction coupling and if contraction occurs only when the intracellular concentration of Ca^{++} exceeds a critical level, then relaxation may reflect a reduction in the intracellular concentration of Ca^{++}, in particular of those Ca^{++} which are available to the myofibrils. In 1952 Marsh reported that homogenates of skeletal muscle inhibited ATP-induced contractions in myofibrils incubated in the presence of Ca^{++} and since then many attempts have been made to isolate and identify the particular component in the homogenate which is responsible for this inhibition. There is general agreement that vesicular fragments of the sarcoplasmic reticulum, but not the "T" system, are primarily responsible for this inhibition of contraction, and that relaxation is associated with or due to the ability of this fraction to accumulate Ca^{++}. Ebashi and Lipmann, Ebashi, Carsten and Mommaerts, Weber and associates, Hasselbach and Makinose, and others have shown that in the presence of Mg^{++} and ATP this vesicular fraction when isolated from skeletal muscle is capable of accumulating Ca^{++} against a large concentration gradient. Weber and associates concluded that in skeletal muscle this vesicular fraction competes successfully with actomyosin for the available Ca^{++} through its mechanism of Ca^{++} accumulation and in so doing promotes relaxation.

Electron micrographs have shown that a well-defined sarcoplasmic reticulum is present in skeletal muscle in close proximity both to the myofibrils and to the transverse tubular system. A similar but less well-defined sarcoplasmic reticulum has been described for cardiac muscle. Inesi and associates separated this fraction from bovine heart muscle and found that it resembled that of skeletal muscle in that, when ATP and Mg^{++} were present, it accumulated Ca^{++}. Others, including Lee, Lee and co-workers, Carsten, and Nayler and Hasker, have confirmed the existence in cardiac muscle of a vesicular fraction which, when isolated and incubated under appropriate conditions, accumulates Ca^{++} at a rate which is not significantly different from that displayed by similar skeletal muscle preparations. The uptake of Ca^{++} by cardiac sarcoplasmic reticulum fraction is enhanced if creatine phosphate and creatine phosphokinase are added to the incubation mixture already containing

Inorganic phosphate (IP) Mg^{++} and ATP [88,44]

If the in situ sarcoplasmic reticulum resembles that isolated from homogenized cardiac muscle then the presently available data favor the hypothesis that in cardiac muscle as in skeletal muscle relaxation reflects the ability of the sarcoplasmic reticulum to accumulate Ca^{++}

Effect of electrical stimulation on Ca^{++} in the sarcoplasmic reticulum

Recently Lee[44,71] passed monophasic square wave pulses through suspensions of sarcoplasmic reticulum isolated by differential centrifugation from homogenates of cardiac muscle and observed a partial inhibition of the uptake of Ca^{++} In addition, he noted that electrical stimulation of Ca^{++}-loaded reticulum fractions resulted in a release of Ca^{++} from the reticulum into the suspending medium Caution must be extended in applying these in vitro findings to in vivo conditions nevertheless they may indicate as Lee has contended that as the wave of excitation travels along the muscle fiber it alters the membrane potential including that of the transverse tubular system which in turn initiates a change in the sarcoplasmic reticulum resulting not only in an inhibition of the accumulation of Ca^{++} but in addition, in a displacement of Ca^{++} from the reticulum into the myoplasm In accordance with this hypothesis, cessation of stimulation is accompanied by the restoration of the ability of the reticulum to accumulate Ca^{++} against a concentration gradient. [72] *Hence in cardiac muscle* at least the sarcoplasmic reticulum may regulate the involvement of Ca^{++} not only in the activation but also *in th* termination of contraction Before this conclusion accepted however at least one other possibility should be considered The so-called sarcoplasmic reticulum fraction when prepared by differential centrifugation of homogenized cardiac muscl may contain in addition to the true sarcoplasmic reticulum fractions derived from the disrupted sarcolemma. If this does happen then Lee may have been recording an excitation-induced displacement of Ca^{++} from the sarcolemmal fragments, as predicted by Niedergerke rather than an excitation-induced release of Ca^{++} from the fragmented reticulum

It is interesting to note that the accumulation of Ca^{++} by cardiac sarcoplasmic reticulum fractions is potentiated in the presence of inorganic phosphate IP [44] Contraction is accompanied by the breakdown of ATP[9,73,74] and the liberation of IP Lee[44] has suggested that, because of the close proximity of the sarcoplasmic reticulum and the myofibrils, contraction probably results in an accumulation of IP in the immediate vicinity of the sarcoplasmic reticulum which may prompt the reticulum to take up Ca^{++} at a faster rate and so precipitate relaxation Drugs and ions which potentiate contractions probably augment the rate at which ATP is broken down and hence the rate at which IP is formed Under these conditions the duration of the weaker contraction may exceed that of the stronger one, with the increased IP formed during the stronger contraction having precipitated the onset of relaxation. These conditions apparently apply during the graded series of contractions which constitute the staircase and throughout the positive inotropic response which follows the addition of extra Ca^{++} to cardiac muscle [72, 4]

Ca^{++} and contraction

The available data indicate therefore that the transition from the resting to the active state is mediated in the presence of ATP by Ca^{++} The energy [77] which permits the interdigitating actin and myosin filaments[7,78] to cyclically form and break their cross-bonds and hence to undergo contraction is provided by the hydrolysis of ATP [79] In the presence of Ca^{++} actomyosin has a very low ATPase activity but actomyosin when present as a Ca complex, hydrolyzes ATP at a rapid rate [80] On this basis it is logical to expect that an increase in the myoplasmic concentration of Ca^{++} will at least under certain conditions facilitate contraction Undoubtedly other proteins, in addition to actin and myosin are involved in this contractile mechanism Recently Ebashi and his colleagues[79] indicated that one such additional protein the tropomyosin-like protein [*] which occurs in skeletal and cardiac muscle cells alike has a tendency to combine with

F-actin. Ebashi reported that myofibrils which have been digested with low concentrations of trypsin become insensitive to Ca^{++} and that their sensitivity to Ca^{++} is restored if the tropomyosin-like protein is added, a finding which suggests that this tropomyosin-like protein may be fundamentally involved in the processes whereby Ca^{++} facilitate contraction. However, as Mommaerts[77] has emphasized, the stoichiometric relation between calcium uptake and ATP splitting in vivo is entirely unknown, and until this is established caution must be exercised in applying such in vitro observations to in vivo conditions, as for example to the contraction-relaxation cycle of cardiac muscle.

Ca^{++} and cardioactive drugs

Once it is established that the contraction-relaxation cycle in cardiac muscle may reflect a relative increase and decrease in myoplasmic Ca^{++}, respectively, the question arises whether cardioactive drugs act on the mechanisms involved in the regulation of myoplasmic Ca^{++} to promote either contraction or relaxation.

Cardiac glycosides

The beneficial effect of cardiac glycosides on heart muscle is already well documented.[78] At the beginning of this century it was generally believed that Ca^{++} were essentially involved in the mechanisms whereby the glycosides strengthen cardiac contractions.[79,80] In 1959 Hajdu and Leonard[81] reviewed the available literature which related to the mode of action of these drugs and concluded that their positive inotropic activity was causally related to a changed cellular K^+, not Ca^{++}. Recent isotope studies, however, not only substantiate the hypothesis that Ca^{++} are essentially involved in the inotropic action of the glycosides,[4] but, in addition, indicate that a reduced K^+ need not necessarily accompany the positive inotropic response.[82-85]

The glycoside-induced increase in contractile force could theoretically reflect an increase in myoplasmic Ca^{++} and hence in the amount of ionized Ca which is available to the myofibrils for participation in contraction. Such an increase in myoplasmic Ca^{++} might be the result of an increase in the resting influx of Ca^{++}, an increase in the influx of Ca^{++} during or in association with excitation, a decreased efflux of Ca^{++}, mobilization of Ca^{++} from intracellular storage sites, including the mitochondria,[86] and a decrease in the capacity of the sarcoplasmic reticulum to accumulate Ca^{++}.[87] Probably several of these mechanisms are involved. Thus, in 1960 Sekul and Holland[88] reported that although ouabain did not change the rate at which Ca^{++} were accumulated by quiescent rabbit atria, the uptake of Ca^{++} by electrically stimulated preparations was increased approximately fivefold when ouabain was present. The concentrations of ouabain which Sekul and Holland used were sufficient to cause the development of contracture; hence their results, which show quite clearly that ouabain does enhance the uptake of Ca^{++} by actively contracting preparations but not by quiescent ones, should be related only to the contracture-producing action of the glycosides and not to their positive inotropic activity. Lullmann and Holland[4] investigated Ca^{45} exchange in isolated guinea pig atria under conditions in which ouabain produced either a positive effect or contracture as required, and found that, although the positive inotropic response was associated with an increase both in the amount of exchangeable Ca^{++} present in the tissue and in the influx of Ca^{++} associated with excitation, the total Ca in the muscle remained constant. Contracture-producing concentrations of ouabain caused, in addition to the increase in exchangeable Ca^{++}, a significant increase in the total tissue Ca. These results[4] are summarized in Table III. Similar changes in cellular and exchangeable Ca^{++} were detected in other studies in which strophanthin K was added to electrically stimulated guinea pig atrial preparations.[89]

In 1965, while investigating the effect of ouabain on Ca^{++} exchange in isolated rabbit atria as a function of the number of contractions which occurred during 5 minutes of exposure to Ca^{45}, Govier and Holland[90] showed that ouabain altered both the rate of Ca^{++} exchange and the size of an as yet unidentified "calcium-pool"[91] which becomes available during

Table III. Effect of ouabain on Ca in isolated spontaneously beating guinea pig atria

Preparation	Ouabain (M)	Duration (min)	Response	Ca^{45} uptake ± S.E. (c.p.m./Kg × 10⁻⁷)	Total tissue Ca ± S.E. (mEq./Kg)	Exchangeable Ca^{++} (mEq./Kg)
Guinea pig atria[44]		60		2 0 ± 0 07	5 2 ± 0 15	0 94
	6 × 10⁻⁷	60	Positive inotropic	2 5 ± 0 18	5 4 ± 0 16	1 24
	2 × 10⁻⁶	60	Contracture	5 4 ± 0 11	6 5 ± 0 15	2 60

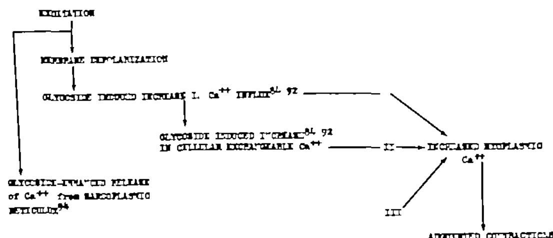


Fig. 3. Glycoside-induced increase in the myoplasmic Ca^{++} and the positive inotropic response. Schematic representation showing the possible cellular sites at which the glycosides may act to increase myoplasmic Ca^{++}.

activation for participation in contraction.[92, 93] These results closely resemble those of Lüllmann and Holland[44] and of Grossman and Furchgott[1] in all of these studies the glycoside-induced increase in the size of the calcium pool is reflected in the increase in the specific activity of the tissue Ca^{++} relative to that found in control preparations.

If as these studies suggest cardiac glycosides increase both the Ca^{++} which is taken up by the muscle cells during excitation and the amount of ionized and therefore exchangeable Ca present in the intracellular "calcium-pool" then their positive inotropic action could reflect the resultant increase in myoplasmic Ca^{++}. The question then arises as to why these additional Ca^{+} are not immediately accumulated by the sarcoplasmic reticulum.[97] Recently Lee and associates[94] demonstrated the occurrence of interaction between cardiac glycosides and the excitation induced release of Ca^{++} from the sarcoplasmic reticulum. The cardiac glycosides appeared to potentiate the effect of electrical stimulation on the release of Ca^{++} from extracted sarcoplasmic reticulum as indicated by the development of tension in the isolated myofibrils. Hence even if in intact cells these additional Ca^{++} were accumulated by the reticulum during relaxation some additional Ca would be released into the myoplasm and hence into the immediate vicinity of the myofibrils during or as the result of excitation.

The mechanism whereby the cardiac glycosides apparently increase the concentration of Ca^{++} within the myoplasm are shown schematically in Fig. 3. It seem

to be probable therefore that the beneficial effect of the glycosides on cardiac contractions can be accounted for in terms of such an increase in myoplasmic Ca^{++}.

Catecholamines

The phosphorylase enzyme which catalyzes the reaction glycogen + inorganic P ⇄ glucose-1-phosphate occurs in two forms, the *a* form which is active in the absence of adenosine monophosphate (AMP) and the *b* form which is active *only if AMP is present.*[30] *Adenosine 3,5 phosphate* (*cyclic 3,5 AMP*) promotes the transformation of the enzyme phosphorylase from the *b* to the *a* form; catecholamines, including norepinephrine and epinephrine, *stimulate the production of* cyclic 3,5 AMP. Many unsuccessful attempts have been made to correlate the effect of catecholamines on the force of myocardial contractions with the changed phosphorylase a/b ratio.[34,35] There is evidence[36,37] however to support a theory that the accumulation of cyclic 3,5 AMP induced by catecholamines is fundamentally associated with their positive inotropic activity. For example β-adrenergic antagonists[38] which block the positive inotropic activity of catecholamines, but not that of other positively inotropic agents, including Ca^{++} and the cardiac glycosides, inhibit the accumulation of cyclic 3,5 AMP. The xanthines potentiate the positive inotropic action of norepinephrine on cardiac muscle[162] and, by inhibiting cyclic phosphodiesterase, cause an accumulation of cyclic 3,5 AMP.

If an intracellular accumulation of 3,5 AMP is fundamentally involved in the positive inotropic action of the catecholamines, then the question arises whether Ca^{++} are involved in the mechanism whereby cyclic 3,5 AMP affects contraction. Presumably Ca^{++} are involved because if they are absent catecholamines do not activate contraction.

Cyclic 3,5 AMP is known to affect a number of enzymes and cellular processes, including membrane permeability.[4] Recently Grossman and Furchgott[44,45] reported that norepinephrine failed to cause any significant change in the exchange of ionized Ca in quiescent guinea pig atria. *The addition of norepinephrine to actively contracting preparations,*[45] however, was associated with a significant increase in the uptake of Ca^{45}. Some of their results are summarized in Table IV. If as these *results suggest, catecholamines enhance* the uptake of Ca^{++} by actively contracting preparations, then it is possible that their positive inotropic activity reflects the resultant increase in intracellular Ca^{++}. *These events are summarized in Fig. 4.*

The role played by cyclic 3,5 AMP in the normal regulation of membrane permeability requires further investigation. Subcellular fractionation of skeletal muscle homogenates has shown that the enzyme adenyl cyclase which is involved in the formation of cyclic 3,5 AMP is localized in fractions which sediment with the Ca^{++} accumulating granules derived from the sarcoplasmic reticulum.[99] *Variations* in the concentration of cyclic 3,5 AMP may be associated, therefore, with the uptake and release of Ca^{++} from the membranous components of this reticulum.

If the positive inotropic action of the cardiac glycosides and catecholamines alike depends upon an elevated intracellular concentration of Ca^{++}, then the fact that only the positive inotropic activity of the

Table IV. Effect of norepinephrine on the uptake of Ca^{45} by electrically stimulated guinea pig atria[45]

Rate (beats/min)	Norepinephrine (M)	Ca^{45} uptake (mmol/Kg/5 min)	Relative amplitude of contractions
6		0.51 ± 0.05	22 ± 4.0
6	1 × 10⁻⁶	0.71 ± 0.08	131 ± 14
60		0.89 ± 0.02	88 ± 4
60	1 × 10	0.97 ± 0.01	182 ± 2.8

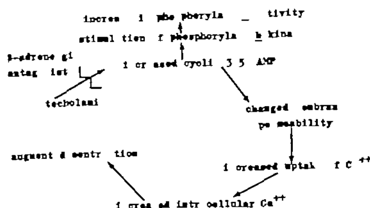


Fig. 4. Schematic representation of the events involved in the action of catecholamines on cardiac contractions.

former[illegible] and not that of the latter[illegible] is associated with an increase in the efficiency with which the heart performs mechanical work requires some explanation. The solution to this problem probably is associated with the *direct* action which the cardiac glycosides have on membrane permeability and Ca^{++} exchange,[illegible] in contrast to the *indirect* action of the catecholamines on membrane permeability which may be mediated via the formation of cyclic 3',5'-AMP as indicated.

Xanthines

The xanthine derivatives, including theophylline, theobromine, caffeine and aminophylline, resemble the cardiac glycosides and catecholamines in that, in the presence of Ca^{++}, they augment cardiac contractions.[illegible] Their positive inotropic activity further resembles that of the catecholamines in that it is associated with an accumulation of cyclic 3',5'-AMP.[illegible] Isotope studies have shown that caffeine increases the rate of Ca^{++} exchange in both skeletal[illegible] and cardiac muscle[illegible] and indicate that the enhanced influx of Ca^{++} which accompanies excitation in xanthine-treated preparations results in a relatively high myoplasmic Ca^{++} and hence in more forceful contractions. The results of other investigations[illegible] indicate that other mechanisms, including the release of ionized Ca from intracellular storage sites[illegible] and an increased resting flux of Ca^{++}[illegible] likewise may be involved in the processes whereby the xanthines increase myoplasmic Ca^{++}. Mitochondrial and microsomal fractions that have been isolated from cardiac muscle which has been immersed in xanthine-enriched physiologic saline solution contain less Ca^{++} than do the mitochondrial and microsomal fractions isolated from control preparations.[illegible]

The mechanisms whereby the xanthines apparently increase myoplasmic Ca^{++} and therefore myocardial contractility are summarized in Fig. 5.

Nicotine

The positive inotropic action of nicotine on cardiac muscle is already well documented.[illegible] Nicotine resembles caffeine in that both drugs not only stimulate the exchange of Ca^{++} across cardiac cell membranes, but in addition facilitate their release from intracellular storage sites.[illegible] The positive inotropic effect of nicotine, therefore, probably reflects an increased myoplasmic Ca^{++} as is shown schematically in Fig. 6. Many other drugs including tetraethylammonium chloride,[illegible] reserpine[illegible] and adenosine[illegible] can be added to the list of drugs which simultaneously influence cardiac contractions and the availability of Ca^{++}.

Effect of cardioactive drugs on the transport of Ca^{++} across a lipid-solvent-aqueous interface

This intracellular accumulation and translocation of Ca^{++} which occurs in association with conditions of increasing contractility reflects the existence of a mechanism for the transport of ionized Ca from an aqueous extracellular phase

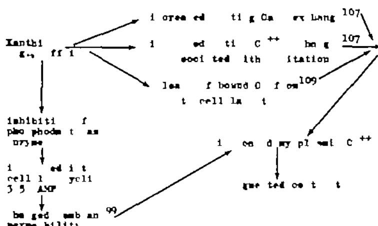


Fig 5 Schematic representation of the action of xanthines on Ca^{++} exchange in cardiac muscle

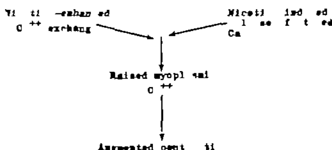


Fig 6 Schematic representation of the events involved in the positive inotropic effect of nicotine on cardiac muscle

through lipid-containing membranes and hence into the myoplasm

Lipids extracted from cell membranes of cardiac[11,11] and other excitable tissues[117,118] facilitate the transport of Ca^{++} across an aqueous-lipid solvent interface Recent studies have shown that some cardioactive drugs interact with this system thus the beta adrenergic receptor blocking drugs pronethalol and propranolol resemble quinidine[11] in that they interact with these lipids, and in so doing inhibit their ability to facilitate the transport of Ca^{++} The sympathomimetic amines epinephrine and norepinephrine[118] react with the lipids to potentiate their Ca^{++} transporting activity The similarity between the antiarrhythmic drugs quinidine pronethalol and propranolol in regard to their interaction with lipids extracted from the membranes of cardiac cells raises the question whether this interaction is related to their antiarrhythmic properties.[11,120] The sympathomimetic-induced potentiation of lipid facilitated Ca^{++} transport possibly may be associated with the well-established ability of these drugs to precipitate cardiac arrhythmias and is in accord with the norepinephrine-induced increase in the uptake of Ca^{++} described by Grossman and Furchgott.[21,22]

Summary

The conclusion that the state of relaxation or strength of contraction in cardiac muscle at any particular instant reflects the concentration of ionized calcium in the myoplasm appears to be inescapable Many cardioactive drugs, including the cardiac glycosides, the sympathomimetic amines adenosine nicotine the xanthines, and the antiarrhythmic drugs quinidine pronethalol and propranolol act in a variety of ways to effect changes in the intracellular concentration and distribution of ionized calcium The available data

support the hypothesis that such drug induced changes in myoplasmic Ca^{++} may be responsible for the cardioactive properties of these drugs.

REFERENCES

1. Harvey W Exercitatio anatomica de motu cordis et sanguinis in animalibus, 1628 Translated by Robert Willis, England, 1847
2. Harvey W Lumleian Lectures, 1616, from Classics of Cardiology Vol. 1 p. 15, edited by Fredrick A. Willius and Thomas E. Keys, New York, 1961 Dover Publications.
3. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart, J Physiol 4:29 1883.
4. Nayler W G. The significance of calcium ions in cardiac excitation and contraction, Am. Heart J 65:404, 1963.
5. Sandow A. Excitation-contraction coupling in skeletal muscle, Pharmacol. Rev 17:265 1965.
6. Heilbrunn, L. V and Wiercinski, F J The action of various cations on muscle protoplasm, J Cell Comp. Physiol. 29 15 1947
7. Huxley H. E.: Muscle cells, in Brachet, J and Mirsky A. E., editors: The cell, New York, 1960, Academic Press, Inc., p. 356.
8. Davies, R. E A molecular theory of muscle contraction. calcium-dependent contractions with hydrogen bond formation plus ATP dependent extensions of part of the myosin-actin cross-bridges, Nature (London) 199 1068, 1963
9. Davies, R. E. On the mechanisms of muscular contraction, in Campbell, P N and Greville, G D editors: Essays in biochemistry Vol 1 p. 29 New York, 1965 Academic Press, Inc.
10. Ebashi, D Calcium binding activity of vesicular relaxing factor J Biochem. (Tokyo) 50:236, 1961
11. Weber A., and Herz R Requirement for calcium in the synaeresis of myofibrils, Biochem. Biophys. Res. Commun. 6:364, 1961.
12. Weber A., and Winicur S. The role of calcium in the superprecipitation of actomyosin, J Biol. Chem. 236:3198, 1961.
13. Woodbury J W Interrelationships between ion transport mechanisms and excitatory events, Fed. Proc. 22:31 1963.
14. Hoffman, B. F and Cranefield, P F: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Co., Inc.
15. Sandow A. Physical and chemical basis of muscular contraction, J Pros. Dent. 14:907 1964.
16. Sandow A. Excitation-contraction coupling in muscular response, Yale. J Biol. & Med. 25 176, 1952.
17. Shanes, A. M. Electrochemical aspects of physiological and pharmacological action in excitable cells, Pharmacol. Rev 10:59 1958.
18. Winegrad, S., and Shanes, A. M.: Calcium flux and contractility in guinea pig atria, J Gen. Physiol. 45:311 1962.
19. Locke, F S., and Rosenheim, O Contributions to the physiology of the isolated heart. The consumption of dextrose by mammalian cardiac muscle, J Physiol. 36:205 1907
20. Mines, G. R. On function analysis by the action of electrolytes, J Physiol. 46 188, 1913.
21. Frank, G. B Calcium and initiation of contraction, Circulation Res. 14 (Suppl. 2):54, 1964.
22. Nayler W G.: Calcium and other divalent ions in contraction of cardiac muscle, in Paul, W. M., et al., editors: First Symposium on Muscle Structure and Function, University of Alberta, p. 167 London, 1965 Pergamon Press.
23. Nayler W G and Emery P F Contractions of ventricular muscle in absence of certain cations, Am. J Physiol. 206:909 1964.
24. Niedergerke, R. Local muscular shortening by intracellularly applied calcium, J Physiol, 134:584, 1955.
25. Podolsky R. J and Constantin, L. L. Regulation by calcium of the contraction and relaxation of muscle fibers, Fed. Proc. 23:933, 1964.
26. Portzehl, H., Caldwell, P C., and Rüegg, J C. The dependence of contraction and relaxation of muscle fibres from the crab, Maia squinado, on the internal concentration of free calcium ions, Biochim Biophys. Acta 79:581 1964.
27. Bianchi, C. P and Shanes, A. M. Calcium influx in skeletal muscle at rest, during activity and during potassium contracture, J Gen. Physiol. 42:803, 1959
28. Grossman, A., and Furchgott, R. F The effects of various drugs on calcium exchange in the isolated guinea-pig left auricle, J Pharmacol. & Exper Therap. 145 162, 1964.
29. Niedergerke, R. Movements of Ca in frog heart ventricles at rest and during contracture, J Physiol. 167:515 1963.
30. Nayler W G. Influx and efflux of calcium in the physiology of muscle contraction, J Clin. Orthopaed. & Related Res. 45:157 1966.
31. Daly I de B and Clark, A. J The action of ions upon the frog heart, J Physiol. 54:367 1921
32. Niedergerke R., and Harris, E. J Accumulation of calcium (or strontium) under conditions of increasing contractility Nature (London) 179 1068, 1957
33. Niedergerke, R. The potassium chloride contracture of the heart and its modification by calcium, J Physiol. 134:584, 1956.
34. Niedergerke, R. Movements of Ca in beating ventricles of the frog, J Physiol. 167:551 1963.
35. Langer G. A. Calcium exchange in dog ventricular muscle Relation to frequency of contraction and maintenance of contractility Circulation. Res. I 78, 1965
36. Langer G. A., and Brady A. J Calcium flux in the mammalian ventricular myocardium, J Gen. Physiol. 46 703 1963.
37. Bowditch, H. P Über die Eigenthümlichkeiten der Reizbarkeit, welche

fasern des Herzens zeigen, Ber Sa hs, Ges. (Akad.) Wiss 1871 p 652.
38 Hodgkin A. L. The ionic basis of electrical activity nerve nd muscle, Biol Rev 26:339 1951
39 Constanti F L. Franzini Armstrong, C and Podolsky R. J Localization of calcium accumulating structures i striated muscle fibers, Science 147 158, 1965.
40. Peachey L. D Structure of the sarcoplasmic reticulum and T-system of triated muscle Proc 23rd International Congress of Physiological Sciences Tokyo, 1:388 1965
41 Huxley H E. Evidence for continuity be tween the central lement of the triads and the extracell lar space in f og sartorius muscle Nature (London) 202 1067 1964
42 Walker S. M and Schrodt G R Membrane like structures within the sarcoplasmic reticulum N ture (London) 206 150, 1965
43. Winegrad, S. Autoradiographic studies of intracellular calcium in frog skeletal muscle J Gen Physiol 48:544 1965.
44 Winegrad, S The location of muscle calcium with respect to the myofibrils, J Gen Physiol. 48:997 1965
45 Winegrad, S The possible role of calcium in excitation-contraction coupling of heart muscle Circulation 24:523 1961
46. Koch Weser J and Blinks, J R The in fluence of the interval between beats on myocardial contract lity Pharmacol Rev 15:601 1963.
47 Lüttgau, H C. and Niedergerke R The antagonism between Ca nd N ions on the frog heart, J Physiol 143:486 1958
48 Wilbrandt W von, nd Koller H Die Calciumwirkung am F oschherzen le Funk tion des Ionengleichgewichts zwischen-zellmembran und Umgebung, Helvet. Physiol. Acta 6:208 1948
49 Langer G A Kinetic studies of calcium distribution entricular muscle of the dog Circulation Res 15:393 1964
50. Douglas, W W and Rubin, R P The mech anism of catecholamine release f om the adrenal med lla and the ole of calcium in timulus-secretion oupling J Physiol. 167 288, 1963
51 Frank, G B Effects of changes in extracellular calcium concentration on the potassium induced contracture of frog skeletal muscle J Physiol. 151:518 1960.
52. Frank G B Evidence for n essential role of calcium in excitation-contraction coupling in skeletal muscle Proc. Roy Soc London, ser B. 160:504 1964
53 Frank, G. B. Utilization of bound calcium in the action of caffeine nd cert in multivalent cations on skeletal muscle J Physiol. 163:254 1962.
54. Nayler W G., nd Anderson, J Effects of zinc on cardiac muscle contraction, Am. J Physiol. 209 17 1965
55 Marsh B. B.: The effects of ATP on the fibre-volume of muscle homogenat Biochim. Biophys. Acta 9:247 1952.
56. Schuel, H Lorand L. Schuel R., and Anderson, N G. Isolation of relaxing particles from rat skeletal muscles in zonal centrifuges, J Gen. Physiol. 48 737 1965
57 Porter K. R. The sarcoplasmic reticulum. Its recent history and present status, J Biophys. Biochem. Cytol. 10:219 1961
58. Seraydarian, S. and Mommaerts, W F H. M Density gradient separation of sarcotubular vesicles and other particulate constituents of rabbit muscle, J Cell. Biol. 26:641 1965.
59 Lee K. S Present status of cardiac relaxing factor Fed. Proc. 24 1432 1965
60 Ebashi, S., and Lipmann, F Adenosine triphosphate-linked concentration of calcium ions in particulat f action of rabbit muscle, J Cell. Biol 14:389 1962.
61 Carsten, M E. and Mommaerts, W F H. M The accum lation of calcium ions by sarcotubular vesicles, J Gen. Physiol. 48 183, 1964.
62. Weber A., Herz, R and Reiss, I: On the mechanisms of the relaxing effect of fragmented sarcoplasmic reticulum, J Gen. Physiol. 46:679 1963.
63 Hasselbach, W and Makinose, M: Über den Mechanismus des Calcium-transportes durch die Membranen des sarcoplasmatischen Reticulums, Biochem Ztschr 339:94, 1963.
64 Porter K. R., and Palade G. E. Studies on the endoplasmic reticulum III Its form and distribution i striated muscle cells, J Biophys. Biochem Cytol 3:269 1957
65 Franzini-Armstrong C. nd Porter K. R.: Sarcolemmal invaginations constituting the T-system in fish muscle fibres, J Cell. Biol. 22:675 1964
66. F wcett, D W The sarcoplasmic reticulum of skeletal and cardiac muscle, Circulation 24:336, 1961
67 Inesi, G Ebashi, S. nd W tanabe, S.: Preparation of vesicular relaxing factor from bovine heart tissue, Am. J Physiol. 207 1339 1964
68. Lee, K. S Ladinsky H., Choi, S. J and Kasuya, Y Studies on the in vitro interac tion of lectrical stimulation and Ca++ movement in sarcoplasmic reticulum J Gen Physiol 49:689 1966.
69 Carsten, M E.: The cardiac calcium pump, Proc. N tional Academy of Sciences 52 1456, 1964
70. N yler W G., and Hasker J Unpublished results, 1966.
71 Lee K S. Effect of electrical stim lation on uptake and release of calcium by the endoplasmic reticulum N ture (London) 207:85, 1965
72. Fanburg B Finkel, R. M and Martinosi, A. The ole of calcium in the mechanism of relaxation of cardiac muscle, J Biol. Chem. 239:2299 1964.
73. Infante, A. A and D vies, R E. Adenosine triphosphate breakdown during single isotonic twitch of f og sartorius muscle, Biochem. Biophys. Res. Comm n. 9 410, 1962.
74 Cain, D F Infante, A. A., and D vies, R. E.:

Chemistry of muscle contraction. Adenosinetriphosphate and phosphorylcreatine as energy supplies for single contractions of working muscle, Nature (London) 196:214 1962.

75 Nayler W G : A study of the "staircase" in ventricular muscle and its relationship t the inotropic activity of certain drugs, J Gen. Physiol. 41:339 1960

76. Brady A. J Abbott, B C., and Mommaerts W F H. M Inotropic effects of trains of impulses applied during contraction of cardiac muscle J Gen. Physiol 44:415 1960.

77 Mommaerts, W F H. M Energetics and chemical mechanism of the primary events in muscular contraction, Proc. 23rd International Congress of Physiological Sciences, Tokyo 4:399 1965.

78 Huxley H. E. Electron microscope studies on the structure of natural and synthetic protein filaments from striated muscle, J Molec. Biol 7:281 1963

79 Ebashi, S. Studies on the contractile system from physiological point of iew Proc. 23rd International Congress of Physiological Sciences, Tokyo 4:405 1965.

80 Hajdu, S and Leonard, E. The cellular basis of cardiac glycoside action, Pharmacol Rev *11 173 1959*

81 Clark, A. J The mode of action of strophanthin upon cardiac tissue J Pharmacol. & Exper Therap 5:215 1913.

82. Loewi, O Über den Zusammenhang zwischen Digitalis-und Kalzium irkung Arch. exper P th. Pharmakol. 82 131 1917

83. Konschegg, A., von. Über Beziehungen zwischen Herzmittel-und physiologischer Kationenwirkung, Arch. exper Path. Pharmakol. 71:251 1913

84. Lüllmann, H and Holland, W Influence of ouabain on an exchangeable calcium fraction, contractile force, nd resting tension of guinea-pig tria, J Pharmacol. & Exper Therap 137 186 1962.

85 Tuttle R. S Witt, P N and Farah, A. The influence of ouabain on intracellular sodium and potassium concentrations in the rabbit myocardium, J Pharmacol. & Exper Therap. 133:281 1961

86. Vick, R L. and Kahn, J B. The effects of ouabain and eratridine on potassium movement in the isolated guinea-pig heart, J Pharmacol & Exper Therap. 121:389 1957

87 T ttle, R. S Witt, P N and Farah A. Therapeutic and toxic effect of ouabain on K fluxes in rabbit tria, J Pharmacol. & Exper Therap. 137 24 1962

88 Rayner B and Weatherall, M.. Digoxin, ouabain and potassium movements in rabbit auricles Brit. J Pharmacol. 12:371 1957

89 Slater E. C., nd Cleland, K. W The effect of calcium on the respiratory nd phosphorylative acti ities of heart muscle sarcosomes. Biochem J 55:566, 1953

90 Sek l, A. A nd Holland, W C. Effects of ouabain on Ca⁴⁵ entry in quiescent and electrically driven rabbi atria, Am J Physiol. 199:437 1960.

91 Govier W C., and Holland, W C. The relationship between trial contractions and the effect of ouabain on contractile strength and calcium exchange in rabbit tria, J Pharmacol & Exper Therap. 148:284 1965.

92. Grossman, A., and Furchgott, R. F The effects of external calcium concentration on the distribution and exchange of calcium in resting and beating guinea-pig auricles, J Pharmacol. & Exper Therap 143 107 1964

93. Grossman, A., and Furchgott, R. E. The effects of frequency of stimulation and calcium concentrations on Ca⁴⁵ exchange and contractility on the isolated guinea-pig auricle J Pharmacol & Exper Therap. 143 120 1964.

94 Lee K. S., Yu, D H., and Struthers, J J A study of the effect of cardiac glycosides on the syneresis of myofibrils in the presence of relaxing factor J Pharmacol. & Exper Therap. 148:227 1965

95 Sutherland, E. W and Rall, T W : The relation of adenosine-3 5 -phosphate and phosphorylase to the actions of catecholamines and other hormones, Pharmacol Rev 12:265 1960.

96. Mayer S. E., Cotten, M d V and Moran, N C. Dissociation of the ugmentation of cardiac contractile force from the activation of myocardial phosphorylase by catecholamines, J Pharmacol. & Exper Therap. 139:275 1963

97 Drummond, G. I Valadares, J R. E., and Duncan, L. Effect of epinephrine on contractile tension and phosphorylase activation in rat and dog hearts, Proc. Soc. Exper Biol. & Med. 11 :307 1964.

98 Williamson, J R. Kinetic studies of epinephrine effects in the perfused rat heart, Pharmacol Rev 18:205 1966.

99 Sutherland, E. W and Robison G A. The role of cyclic 3 5 AMP in responses to catecholamines and other hormones, Pharmacol. Rev 18 145 1966.

100. Levine, R. A. Cardiovascular and metabolic effects of adenosine 3 5' monophosphate in man, J Clin. Invest. 44 1068, 1965

101 Ahlquist, R. P A study of the adrenotropic receptors, Am. J Physiol. 153:586 1948.

102. Rall, T W and West, T C The potentiation of cardiac inotropic responses to nor epinephrine by theophylline, J Pharmacol & Exper Therap. 139:269 1963.

103 Nayler W G. The action of strophanthin G nd digoxin on energy production in the isolated toad heart, Australia J Exper Biol & M Sc. 31:377 1956.

104 Nayler W G The action of adrenaline and noradrenaline on the isolated toad heart, Australia J Exper Biol & M Sc. 31:247 1956

105 De Gubareff T and Sleator W Effect of caffeine on mammalian trial muscle, and its interaction with adenosine and calcium, J Pharmacol & Exper Therap. 148:202, 1965

106 Bianchi, C. P The effect of caffeine on radiocalcium movement in frog sartorius, J Gen Physiol. 44:845 1961

107 N yler W G Effect of caffeine on cardiac contractile activity and radiocalcium movement, Am. J Physiol. 204:969 1963

108. Frank, G. B. Utilization of bound calcium in the action of caffeine and certain multivalent cations on skeletal muscle, J Physiol. 163:254 1962.

109 Nayler W G and Hasker J R. Effect of caffeine on calcium in subcellular fractions of cardiac muscle, Am. J Physiol. 211:950 1966.

110 Cheney R. H Ventricular response in caffeine-nicotine antagonism, J Pharmacol. & Exper Therap. 54:42 1935

111 N yler W G Effect of icotine on cardiac muscle contractions and radiocalcium movement, Am. J Physiol. 205:890, 1963.

112. N yler W G., and Emery P F: Nicotine-induced contractures in depolarised cardiac muscle Arch. Int. Pharmacodyn. 153:283, 1965

113. N yler W G and Emery P F The positive inotropic activity of tetraethylammonium ions and their effect on radiocalcium movement, J Pharmacol. & Exper Therap. 144 116, 1964

114. N yler W G. A direct effect of reserpine on ventricular contractility J Pharmacol. & Exper Therap. 139:222, 1963

115 Nayler W G. An effect of quinidine sulphate on the lipid-facilitated transport of calcium ions in cardiac muscle, Am. Heart J 71:363 1966.

116 Nayler W G. The effect of pronethalol and propranolol on lipid-facilitated transport of calcium ions, J Pharmacol. & Exper Therap. 153:479 1966.

117 Woolley D W Transport of calcium through cell membranes as mediated by certain hormones, in Wasserman, R. H., editor: Transfer of calcium and strontium across biological membranes, New York, 1963 Academic Press, Inc.

118. Feinstein, M B. Reaction of local anesthetics with phospholipids, J Gen. Physiol. 48:357 1964

119 Irons G. V and Orgain, E. S.: Digitalis-induced arrhythmias and their management, Prog Cardiovas. Dis. 8:539 1966.

120 Stock, J P P: Beta adrenergic receptor blockade in cardiac arrhythmias, Brit. M J 2:1230, 1963

Fundamentals of clinical cardiology

The spectrum of Ebstein s anomaly

Edward Genton M.D
S Gilbert Blount J M.D
Denver Colo

Nearly 300 cases of Ebstein s anomaly have been recorded in the literature since its description 100 years ago Most of those cases correctly diagnosed in life have been "typical and it is apparent that this condition is still frequently un recognized especially when some of the typical features are lacking Seventeen patients with Ebstein s anomaly evalu ated at Colorado General Hospital re vealed an interesting spectrum and form the subject of this report. Six of these cases were confirmed at autopsy and the other 11 were suspected on clinical grounds. Of the autopsied cases, 2 were correctly diagnosed during life, whereas death in the other 4 occurred w thout the patient having been seen by the cardiology service The clinical summary of each case is pre sented briefly in order to emphasize par ticular features.

Clinical summaries

Case 1 (CGH #241924) was stillborn female infa t delivered at term to an 18-year-old primi gravida after an unremarkable pregnancy Fetal heart tones had ceased 3 hours before delivery At topsy there as hyperemia of most structures, and effusions in the pleural, pericardial, and peri toneal compartments. The heart eighed 31 grams (normal 20), and the right trium was described as being enormous (4.5 by 3.5 by 3.0 cm.). The tricuspid alve was typically deformed nd there as a patent foramen ovale in addition to patent ductus arteriosus and 2 3-mm ventricular septal defect.

COMMENT It is not certain that the Ebstein mal formation resulted in the death of this child. How ever no other cause for the severe congestiv failure was found. The ventricular septal defect is unusual as will be mentioned

Case (CGH #6129) was 6-week premature infant bo eighed 1,900 grams. She was noted to be cyanotic from birth and had numerous spells of apnea before her death at the age of 5 days. \ heart murmur was described. At autopsy there was hyaline membrane involvement of the lungs nd severe cerebral hemorrhage. The heart weighed 11 5 grams and had typical Ebstein malformation of the tricuspid valve

COMMENT Again, the significance of the con genital heart disease is not certain It would seem to be less factor tha in Case 1

Case 3 (CGH #97278) was the 1 900-gram pre mature female infant of a 15-year-old primigravida with severe pre-eclampsia. The child was cyanotic from birth, and Grade 4/6 systolic murmur was heard over the entire precordium but not described in detail. Progressive cardiac failure ensued, and she died t 4 days of age. At utopsy the onl bnormalities, save for those resulting from con gestive failure, ere found in the heart The organ weighed 23.5 grams (normal 14.65 gram) and re vealed hanges of severe Ebstein malformation of the tricuspid alv ith an associated patent foramen ovale nd a huge right trium.

COMMENT The congenital heart disease seemingl was responsible for the congestive heart failure and death in this ery young child.

Case 4 (CGH #158773), 2-year-old female in fant, was the product of pregnancy complica ed only by an excessive gain in eight. The child as cyanotic t birth and required 20 to 25 minutes of

From the Division of Cardiology Department of Medicine, University of Colorado Medical Center Denver Colo
Supported in part by United States Public Health Service Grant N HE-3390 08
Received for publication Sept. 6, 1966
Address University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 80220

resuscitation. A murmur was heard at birth and thereafter. Growth and development were within normal limits. When she was 1 year old, cyanosis with crying, dyspnea on exertion, and apparent easy fatigability appeared. On examination at rest, the patient revealed duskiness without cyanosis or clubbing, slight cardiac enlargement, a scratchy Grade 2/6 systolic murmur, and a prominent third heart sound. The x-ray film revealed right atrial enlargement, and the electrocardiogram was typical.

COMMENT. The child was cyanotic at birth but not again until 1 year of age, and then only with exertion. The scratchy systolic murmur, third sound, and characteristic electrocardiogram are noteworthy.

Case 5 (CGH #164104) was a 4-year-old American Indian girl in whom a heart murmur had been heard when she was 10 months old and in whom cyanosis at rest was first appreciated when she was 3 years old. She was in the tenth percentile for height and weight but apparently had no physical limitations that were noticeable to the parents. The patient had three bouts of pneumonia after the age of 1 year. On examination, cyanosis and early clubbing were present. The heart was enlarged and a fine precordial thrill was noted in addition to an early systolic click, a Grade 2/6 blowing systolic murmur, a low-pitched apical diastolic murmur, wide splitting of the second heart sound, and a loud third sound. The electrocardiogram was typical, and the x-ray film revealed a very prominent right atrium. Catheterization confirmed the diagnosis of Ebstein's anomaly.

COMMENT. This patient was underdeveloped physically and had clubbing. She had prominent systolic and diastolic murmurs, a sound in systole which timed as an ejection click, a loud third heart sound, and a "typical" electrocardiogram.

Case 6 (#117083), an 8-year-old girl, was the product of a normal pregnancy and was in the twenty-fifth percentile for height and weight. She did well until the age of 4 years, when cyanosis after crying and an active precordium after exercise were noted. Ankle edema and 2-pillow orthopnea occurred at that time, and she improved with digitalis. When she was 8 years old, over a 2-month period edema reappeared, hepatomegaly developed, her condition rapidly deteriorated, and she died in congestive failure. Examination revealed cyanosis without clubbing, malar flush, prominent CV waves in the neck, and prominence of the left precordium. There was cardiac enlargement, wide splitting of both the first and second heart sounds, third and fourth heart sounds, and a Grade 3/6 rough systolic murmur. The x-ray film revealed cardiac enlargement with a large right atrium and narrow pedicle. The electrocardiogram demonstrated a pre-excitation pattern. Catheterization was compatible with the diagnosis of Ebstein's anomaly. At autopsy Ebstein's malformation of the tricuspid valve was confirmed. In addition, hemopericardium (400 c.c.) and right atrial epicarditis were present.

COMMENT. The malar flush, bulging precordium, splitting of heart sounds, gallops, and rough systolic murmur plus the electrocardiographic evidence of pre-excitation and early onset of heart failure are noteworthy. The pathologic findings will be discussed.

Case 7 (CGH #119365), a 12-year-old boy, was cyanotic for a few days in the postnatal period but thereafter appeared to be well. His growth and development were within normal limits until the age of 5 years, when cyanosis appeared after excitement. A murmur was first described when he was 6 years old, at which time he began to squat and became dyspneic and fatigued with exertion. Examination revealed a small young boy in the tenth percentile of growth with cyanosis and early clubbing. There was conjunctival injection and a malar flush. Prominence of the chest bilaterally at the level of the sternal angle was noted, and a thrill was felt in the second and third intercostal spaces out from the sternal border, where there was a diffuse heaving activity. The first heart sound was followed by a click in early systole, and the second heart sound by a high-pitched sound. A Grade 3/6 medium-pitched holosystolic murmur over the precordium and a late diastolic murmur were heard. The electrocardiogram was typical, and the x-ray film revealed slight cardiac enlargement, an enlarged right atrium, and a narrow pedicle. Arterial oxygen saturation was 88 per cent.

COMMENT. Noteworthy are the neonatal cyanosis, which cleared but then returned in childhood, early clubbing, squatting, and malar flush. On examination the clicking systolic sounds and high-pitched early diastolic sound, along with the holosystolic and late diastolic murmurs, are important.

Case 8 (#126701), a 13-year-old girl, was first seen 1 year prior to her death (when she was referred for follow-up by Dr. A. Nadas of Children's Medical Center, Boston, with the diagnosis of Ebstein's anomaly). The child had been cyanotic from birth and had always had fatigue and dyspnea with exertion. In addition, exercise frequently produced retrosternal aching pain, and she often complained of severe nonthrobbing bifrontal headaches that lasted 15 to 30 minutes. Congestive failure occurred when she was 7 years old and responded to digitalis. When she was 13 years old, she developed sharp precordial and left shoulder pain and congestive heart failure, and died suddenly in the hospital. Examination had revealed that she was in the twenty-fifth percentile of growth; there was clubbing, cyanosis, malar flush, pulsus alternans, elevated jugular venous pressure with prominent "V" waves, and bulging of the left precordial heaving wall. There was a thrill along the left sternal border. The heart was active and very much enlarged. The heart sounds were of poor quality and blurred, and a diffuse blowing systolic and scratchy early diastolic murmur was heard, giving a to-and-fro quality. The x-ray film demonstrated a huge globe-shaped heart with a narrow pedicle. The right atrium was markedly enlarged. The electrocardiogram was typical. Autopsy confirmed the diagnosis of Ebstein's anomaly with a patent foramen ovale. In addition there were 50 c.c. of less yellow pericardial fluid and pericarditis, which appeared to be old and fibrous, overlaying the right atrium.

COMMENT. Noteworthy in this case was the early

cyanosis, w th marked limitation of activity throughout lif chest pain, elevated jugular enous pressure ith prominent "V" w es slurred heart tones, to-and-fro murmurs and autopsy evidence of pericarditis. Congestiv heart failure 6 years preceding death is significant.

Case 9 (CGH #19 174), a 13-year-old girl w th normal nonidentical twin had had a murmur t birth, and cyanosis had been appreciated when she as 5 days old. She gained eight poorly and had had several spells of acute dyspnea with cyanosis, flaccid ty nd semiconsciousness bet een the ages of 6 months nd 2 years She alway tried easily nd had dyspnea on exertion At the age of 1 years, she had the first of several bouts of rapid heart action. She as cy notic but ithout lubbing, nd had mild malar flush. The jugular enous pressure was normal, but prominent "V" e as present A thrill was present along the left sternal border nd moderat cardiac enlargement, th long medium-pitched scratchy systolic mur mur and peculia heart sound in early diastole, ere noted. An electrocardiogram taken hen she w 2 eeks old showed normal QRS duration hich had become typical" of Ebstein anomaly by the time she as years old. The x-ray film revealed cardiac enlargement, big right trium nd narrow pedicle Cardiac catheterization hen she as 5 years old compatible ith the diag nosis

COMMENT This patient had normal twin and as cyanotic f om birth She had bouts of tachy cardia nd exercise intolerance and spells of unconsciousness. Note the malar flush lubbing, "V" av scratchy murmur and peculiar diastolic sound Of great importance is the normal QRS duration on the electrocardiogram in early lif

Case 10 (CGH #3541), an 18-yea -old college sophomore, had had murmur t birth but he enjoyed normal health except that he tired more easily tha did his friends W th marked exercise he had some dyspnea nd sharp pain across the precordium H as h ys observed to be mildl cyanotic and this increased on exposure to cold. He had noted frequent bouts of tachycardia f om earl childhood On examination, there was cy nosis minimal clubbing, malar flush, prominent V av in the neck, and slightly prominent precordium A sy olic thrill and y motion t he pex ere present. The heart was enlarged nd scratchy blowing systolic nd mid-diastolic murmur ere heard in addition t a third heart sound The -ra film revealed big right trium globe-shaped heart, nd narrow pedicle The electr cardiogram as "typical" and catheteriza ion ompatible th the diagnosis of Ebstein anomaly

COMMENT Lifelong cy nosis, dyspnea on exer n precordial pain ith exercise and bouts of tach ardia ere prominent in the history Not the malar flush small thrill, and y" acth th scr tchy sy tolic nd mid-diastolic mur murs

Case 11 (CGH #34309) an 18-year-old young man, had first been observed t be cyanotic hen he 2 ears old and he had lway seemed to tir easily nd become dyspneic on exertion. No progression of symptoms occurred for 13 or 14 years. Examination revealed cyanotic young ma ith lubbing a left precordial bulge, slight cardiac enlargement, faint thrill long the left sternal border and harsh loud systolic murm over the entire precordium. The x-ray film demonstrated slight cardiac enlargement, with prominent right atrium and narrow pedicle. The electrocardiogram was "typical. Catheterization confirmed the diagnosis.

COMMENT The combination in this patient of cyanosis with fair exercise tolerance some cardiac enlargement a soft thrill, and peculiar systolic murmur associated ith a typical" electrocardiogram should be noted.

Case 12 (CGH #8989)*, an 18-year-old young man, born of a normal pregnancy and delivery as first noted t be cyanotic t the age of 3 years hen murmur was heard. The cyanosis as obvious only during cold eather or after exercise. H experienced dyspnea after one block and complained of occasional pain in the left side of the chest after exertion. When he as 12 years old pulmon tuberculosis w discovered nd responded medical therapy Physically he was cy notic, with clubbing, and small (t enty-fifth percentile) Ther as chicken-breast deformit with the left precordium being even more prominent than the right. Cardiac enlargement, short systolic mur mur and low-pitched pre-diastolic murmur were present. The second heart sound as split nd did not close and was followed by prominent third sound. The electrocardiogram as typical The chest x-ray film revealed cardiac enlargemen with right trial and right entricular enlargement and narrow pedicle Cardiac catheterization when he was 16 years old confirmed the clinical diagnosis of Ebstein anomaly

COMMENT I this case, the onset of cyanosis after cold nd exercise in early childhood, chest pain, and dyspnea are emphasized The physical underdevelopment chest deformity splitting of heart tones, murmurs and gallops ill be commented upon. The patient had tuberculos

Case 13 (CGH #75744), 28-year-old hite man, had had heart murmur from birth nd tired somewhat more easily than did his peers In spite of this, he did heavy labor u til the age of 23 hen dyspnea on exertion began and he noted that hi lips became blue during exposure to old When he was 24 years old, paroxysmal trial fibrillation dev loped A brai abscess in the right frontoparietal rea hen he as 26 ears old produced hemiparesis and req ired surgical drainage Complete recovery followed ery storm course Atrial fibrillation became fixed hen he as 27 and peripheral edema nd rather marked ease of fatigue had developed by the age of 28 Ph sical examina tion revealed plethoric man th malar flush cardiac enlargement, and pseudo-thrill t he apex The first heart sound loud and fol lowed by ejection click The second heart sound as not prominent Scratch tolic and diastolic murmurs nd third sound were no ed The electrocardiogram as pical as the chest film Cardiac catheterization hen he 21 years old as consistent h he diagnosis of

Ebstein's anomaly and was complicated by atrial fibrillation during the procedure.

COMMENT. This most interesting patient remained acyanotic, but developed atrial fibrillation and signs of failure. During his course a brain abscess occurred. The *pseudo-thrill ejection click*, characteristic quality murmurs, and malar flush are to be noted.

Case 14 (*CGH #131260*) was a 33-year-old man in whom a murmur had first been heard when he was 13. He remained asymptomatic until dyspnea on exertion occurred at age 28 while he was performing heavy work at high altitude (9,300 feet). By age 30 he experienced easy fatigue and dyspnea after 2 or 3 blocks of walking. In addition, occasional shooting precordial pains followed exercise. Examination revealed malar flush, cardiac enlargement and lat ng activity over the precordium, and a rough holosystolic murmur. *The second sound was* widely split and fixed and of decreased intensity. The electrocardiogram and chest film were typical, and cardiac catheterization confirmed the clinical *impression of* Ebstein's anomaly.

COMMENT. The late onset of symptoms and precordial pain are interesting. There was malar flush without cyanosis.

Case 15 (*CGH #68056*), a 47-year-old woman had first been told of a murmur when she was 26, after she had noted bouts of tachycardia for about 6 years. In addition she described an occasional tight feeling high in the anterior chest beneath the clavicles, *after exercise*, that *would last several days*. She pursued normal activities but noted a slowly progressive increase of fatigability, dyspnea on exertion, and more frequent bouts of tachycardia. Also, mild peripheral cyanosis developed during cold weather. On examination, she had a malar flush, a precordial presystolic thrill, and a heaving sensation along the left sternal border. There was cardiac enlargement, the first and second heart sounds were split and loud, and a third sound was heard. Systolic and diastolic murmurs were appreciated. The electrocardiogram was typical, and the chest film revealed a large heart with prominence of the right *atrium and ventricle*.

COMMENT. The late appreciation of a murmur, bouts of tachycardia, chest discomfort, and cyanosis with exposure to cold are to be emphasized. This patient also had a malar flush, systolic and diastolic murmurs, a third sound, and a diastolic thrill. She had splitting of both the first and second heart sounds, and in this case pulmonary closure was thought to be loud.

Case 16 (*CGH #183595*), a 53-year-old electrician, had been told of a heart murmur when he was 8 years old. He noted mild dyspnea with exertion and perhaps ease of fatigability compared to his peers, but was able to work hard. When he was 46 years old, his symptoms increased, and first required that he reduce his work day and finally that he abandon his vocation, at age 53. From age 52 onward, he noted occasional bouts of tachycardia, documented to be atrial fibrillation. On examination he had systemic hypertension (165/120 mm. Hg), malar flush, injected conjunctivae, and an und lating activity over the precordium. The first heart sound was loud and scratchy, *but the second* heart sound was normal. A prominent thrill and fourth heart sound were present. There were no murmurs. The electrocardiogram was typical, and the chest film revealed a narrow pedicle, lack of prominence of the pulmonary artery, cardiac enlargement, and a big right atrium.

COMMENT. Although mild dyspnea with exertion existed from childhood, significant symptoms which were progressive occurred only in the mid-forties. His bouts of tachycardia (fibrillation), malar flush, loud scratchy first heart sound, and the absence of murmurs are to be noted. He remained acyanotic.

Case 17 (*CGH #144497*), a 64-year-old man, had never been aware of cyanosis or a heart murmur. From about the age of 4 years, he had had bouts of regular rapid heart action, lasting from a few minutes to as long as an hour, which ceased spontaneously. At the age of 52, he had had a syncopal spell during such an attack, but otherwise tolerated them well and simply rested until they were over. Quinidine therapy failed to affect them. He worked as a bank teller until his late fifties, without difficulty, although he always tired easily, had dyspnea with marked exertion, and required more sleep than other persons who were his age. He was known to have had systemic hypertension for years. When he was 63, his dyspnea on exertion progressed gradually and finally became very disabling. He then developed ankle edema, orthopnea, and epigastric pain. He was first seen at Colorado General Hospital at the age of 64 years, in congestive heart failure. Examination revealed a blood pressure of 200/120 mm. Hg. He was ruddy faced but did not have clubbing or recognized cyanosis. The fundi revealed hypertensive vascular changes and several flame-shaped hemorrhages (Grade III Keith-Wagener). The jugular venous pressure was elevated without prominence of "A" waves. The heart was enlarged, without thrills, thrusts, or shocks, but with a suggested right ventricular lift. A high pitched holosystolic murmur was heard at the apex, as was a protodiastolic gallop. The liver was enlarged, and ankle edema was present. His electrocardiogram revealed voltage of left ventricular enlargement and repeated supraventricular tachycardia. The QRS configuration and duration was noted to change at different times. Usually it revealed a left bundle branch block; however, at times it was normal, and occasionally during an arrhythmia a "typical" right bundle branch block of Ebstein's anomaly appeared. Chest x-ray films revealed bilateral pulmonary densities in the bases and a cardiac silhouette that was big because of left ventricular enlargement. The patient had repeated bouts of tachycardia during which he became cyanotic, dyspneic, and semistuporous. During one of them, he developed intractable pulmonary edema and hypotension and died. Autopsy revealed left ventricular enlargement and slight thickening of the mitral valve. The tricuspid valve had the typical Ebstein deformity, reducing the functional right ventricle to no more than the outflow tract.

COMMENT. The patient's age, lifelong bouts of tachycardia and dyspnea on exertion, but only late onset of disabling symptoms are of interest. He remained acyanotic. In addition his electro-

Table I. History in patients with Ebstein s anomaly

Case	Development			Symptoms					
	Age	Mental	Physical	Cyanosis	Dyspnea	Fatigue	Arrhythmia	Failure	Pain
1. M	Stillborn	—	—	—	—	—	—	—	—
2. L.	3 day	—	—	Birth	Birth	—	0	Age 3 day	—
3. M	4 days	—	—	Birth	Age 4 day	—	0	Age 4 day	—
4. I G.	2 yr	N	N	Birth and age 1 yr	Age 1 yr	Age 1	0	0	—
5. J U	4 yr	N	Small	Age 3 y	0	0	0	0	—
6. G.S.	8 yr	N	25%	Age 4 yr	Age 4 y	2+	0	Age 4 y	—
7. O.L.	12 yr	N	10%	Age 5 yr	Age 6 yr	2+	0	0	0
8. S.S.	13 yr	N	10%	Birth	Child	2+	0	Age 7 yr	+
9. E.K.	13 yr	N	Small	Birth	Age 6 mo.	2+	12	0	0
10. K.S.	18 yr	N	Thin	Age 7 y	Age 7 yr	2+	Child	0	+
11. T R.	18 yr	N	N	Age 2 yr	Age 2 y	2+	0	0	0
12. P.Mc.	18 yr	N	50%	Age 5 yr	Age 5 yr	2+	0	0	+
13. L.B	28 yr	N	N	Age 23 yr	Age 23 y	2+	Age 24	Age 28 y	+
14. C W	33 yr	N	Slight	0	Age 28 yr	1+	0	0	+
15. I P	47 yr	N	N	0	Age 27 yr	2+	Age 29	0	+
16. H.A.	53 yr	N	Slight	0	Age 8 yr	2+	Age 53	0	0
17. R.B.	64 yr	N	Slight	0	Child	3+	Age 4	Age 64 yr	0

N, Normal. %, Growth percentile. 0, None

cardiogram, which at times revealed normal QRS and at other times right bundle branch block and left bundle branch block, should be noted.

Clinical evaluation

A. Age and sex. The finding in this series of approximately equal distribution of females (9) and males (8) is in keeping with previous reports (Table I).

A unique feature of this series is the spectrum in age. Case 1 died several hours before birth and the autopsy findings strongly suggested that the tricuspid malformation was incompatible with life. Case 2 probably died of prematurity and respiratory distress syndrome, with the congenital heart lesion being incidental. The 4-day-old infant who died in congestive heart failure (Case 3) most certainly died of hemodynamic alterations resulting from the Ebstein malformation. A hiatus then exists in our series, in that the next youngest patient was the 8-year-old girl (Case 6) who pursued a progressively downhill course and died in congestive heart failure.

In this as in other series the majority of patients alive or dead has been in the second to fourth decades. They are quite similar clinically and most of the comments concerning this entity in the literature pertain to patients in this age group since they represent the typical case. Quite different is the small group of patients over the age of 50 years. To date 12 such patients, including 2 in this series have been reported on, comprising only approximately 5 per cent of the total. As will be pointed out, this group is atypi cal in almost every way and the diagnosis may often be missed until the time of autopsy.

B. Family history. A single family has recently been reported with 2 members having Ebstein anomaly. Another patient had a brother with an unknown type of heart disease who died during exertion. Case 9 of the present series had a nonidentical twin who was normal. As with other series, our patients have been the products of normal pregnancies, and no predisposing prenatal factors have been appreciated.

C. History. (See Table I—growth and development.) Mental development in the patient with Ebsteı s anomaly is quite normal. Mental deficiency has been reported and was present in 1 of this series.

(Case 12) Physically the patient with Ebstein's anomaly is usually although by no means always small of stature or slightly built It has been our impression contrary to the opinion of others that the degree of physical retardation correlates rather well with the severity of the cardiac symptoms

D Symptoms

1 CYANOSIS Seventy-eight per cent of this series were cyanotic at some time in their course which is consistent with previous reports [21,22] The intensity and time of onset varied greatly with 30 per cent of the patients being cyanotic from birth and with the majority of others developing cyanosis by the age of 5 years. Often cyanosis was minimal or absent after the first few days of life except during exercise fatigue or cold weather This may actually be considered to be a feature of Ebstein's anomaly since it has been repeatedly mentioned [2] and thought by some to result from a decrease in right-to-left shunting at the atrial level as pulmonary pressure falls in the postnatal period If we disregard the one patient (Case 17) in this series who had only terminal cyanosis which could have resulted from shock and pulmonary infarction the oldest of our patients developing cyanosis for the first time was 23 years old (Case 13) This is not uncommon and many patients develop it only in middle age and one not until the age of 49 Apparently the presence or degree of cyanosis correlates poorly with exercise tolerance since several of our patients who are quite active have marked cyanosis whereas others who are acyanotic suffer from marked physical limitation The 4 oldest patients in this series belong to the acyanotic group of Ebstein's anomaly but since 3 are living it is possible that they will become cyanotic later in their lives. Approximately 15 per cent of patients will remain acyanotic throughout their course These do not represent only those with intact atrial septa since several patients are reported who have a significantly patent foramen ovale without desaturation[19] or with left to-right shunting [2,3]

2. DYSPNEA AND EASY FATIGABILITY This combination of symptoms unfortunately nonspecific must certainly be the most common and often the only complaint of patients with Ebstein's anomaly [1-4] It was present in all except one of the present series regardless of age sex or cyanosis. It is usually apparent within the first year of life may gradually worsen throughout life but generally remains mild unless congestive failure develops terminally Nocturnal dyspnea is, of course rare

3 PALPITATIONS Thirty-six per cent of our patients complained of bouts of palpitations which were documented to be atrial tachycardia or fibrillation. The youngest patient with an arrhythmia was 12 years old (Case 9) although one patient (Case 17) gave a history of paroxysms for 60 years starting at the age of 4 Three in this series described the initial episode of tachycardia only after 20 years of age and one not until the age of 52. It is interesting that our only patient with electrocardiographic evidence of pre-excitation died at the age of 8 without ever complaining of palpitations or having had an arrhythmia observed The occurrence of palpitations in other series varied [4,20,30] between 10 and 33 per cent and resulted from atrial tachycardia flutter or fibrillation which first appeared during infancy or not until adulthood [4]

4 PAIN This most peculiar symptom was noted in 6 of 13 patients old enough to report it. Previous authors found it to occur in 0 to 66 per cent of cases. [19,20] The pain is often precipitated or aggravated by exertion or cold weather and varies in its location and quality Some patients felt it high in the epigastrium others, substernally and still other high in the right or left anterior chest. It has been described as sharp cramping stabbing or shooting The etiology of this pain remains obscure and it may be noted for years without progression Case 13 had chest pain and at autopsy had evidence of rather severe fibrinous pericarditis overlying the right atrium Such findings have been noted previously [12,21] It is conceivable that the pain arises from a pericardium irritated by the presence of fibrin the etiology of which is obscure

E. Physical findings (Table II)

1 MALAR FLUSH Nine of our patients had this peculiar finding and the terms

Table II. Physical findings in patients with Ebstein's anomaly

Case	Age	Cyanosis	Clubbing	Malar flush	Precordial deformity	Thrill	Heart		Sounds						Murmurs		Neck veins
							Size	Ictus	S_1	S_2	S_3	S_4	EC	OS	Systolic	Diastolic	
1 M	5½ Hours	—	—	—	—	—	4+	—	—	—	—	—	—	—	—	—	—
2 L	3 days	+	0	0	0	0	1+	?	?			?			0	0	?
3 M	4 days	+	0	0	+	+	4+	↑	?	↑					+	0	?
4 JG	2 y	—	0	0	0	0	1+	↘	—	↘	+	—			+	0	?
5 JL	4	—	—	0	0	+	3+	↑	—	↘	+	—	+		+	+	↘
6 GS	8 y	0	0	—	+	0	4+	↑	—	N	+	—	+		+	0	↑CV
7 OL	12 y	—	—	+	+	0	4+	↓	↑	↓	+	+	+	+	+	+	N
8 SS	13 y	+	+	+	+	+	4+	↑	↑	↓	+	+			+	+	↑CV
9 IK	15 y	+	0	—	+	+	4+	↑	↘	↓	+	—			+	+	↑CV
10 KS	18	+	+	+	+	+	4+	↓	—	↓	+	—			+	+	↑A
11 TK	18 y	+	+		+	+	1+	↘	—	↓	0	—			+	0	↘
12 PM	18 y	+	+		+	0	4+		—	↑	+	—			+	+	—
13 IB	28 y	0	0	+	+	+	4+	↑	↑	↓	+	—	+		+	+	—
14 CW	31	0	0	+	0	0	4+	↑	N	↓	0	—			+	0	↘
15 II	47	0	0	+	0	0	3+	?	↑	↑	+	—			+	+	—
16 HN	53 y	—	0	+	+	0	1+	↓	↑	↓	+	+			0	0	↑CV
17 RB	61	—	0	+	0	0	2+	↑	—	↘	+	0			+	0	↑?

N Normal ... / Ejection click ... Opening snap

used to describe it by examining physicians included "malar flush," "ruddy faced," and "violaceous hue." The other patients were either neonates, under 4 years of age, or had no comment made concerning the malar eminences. Several reported that their attention had been called to their facial coloration by friends and family throughout life and explained that they had been thought to look healthy. Previous authors have called attention to this finding[20, 38] in a significant number of patients over the age of 2½ years. Its cause is uncertain and does not depend upon the patient being cyanotic or polycythemic.

2. PULSES. The arterial pulse is not characteristically affected in patients with Ebstein's anomaly. In several of our patients it has been considered to be small but of normal contour. Venous activity in regard to the deep jugular system was commented upon in 9 of our cases. In 3 of these it was considered to be normal. Four patients had prominence of the "CV" waves with normal "A" waves, and in only one patient was a prominent "A" wave recorded. The jugular pulse had not been mentioned frequently in the literature in association with patients who have Ebstein's anomaly. In several patients in failure, prominent "V" waves have been recorded, and at least one was noted to have increased "A" and "V" wave, but jugular venous pressures have usually been normal.[38] One might reasonably expect to find with regularity a prominent "A" wave produced by contration of the huge right atrium that is so characteristic of the lesion. In addition, a "CV" wave should exist, since part of the ventricle is located above the tricuspid valve and its contraction should move blood into the atrium and thence into the jugular system. This has been termed an "S" wave by some authors.[41] These expected findings are infrequently seen for several possible reasons. First, it has been noted that right atrial pressure is generally not high in these patients. This is thought to be due to the fact that the atrial walls are thin and toneless.[1] Studies in our patients, however, have demonstrated transmission of a presence wave synchronous with atrial contraction that may even be recorded in the pulmonary artery, thus demonstrating that significant pressures are generated by atrial contraction.[23] An alternate explanation is that the thinned-out toneless wall of the atrialized right ventricle accepts blood during atrial contractions and prevents retrograde propagation of an "A" or "V" wave into the cavae.[7]

3. PRECORDIUM. Three findings apparent on inspection or palpation of the precordium have been noted and suggest the diagnosis. The first is deformity found in 10 patients in this series. In 9 of these it consisted of a bulging of the left precordium as compared to the right. The appearance was similar to that seen in patients with other types of congenital heart disease, especially atrial or ventricular septal defects associated with left-to-right shunting. One patient (Case 13) had bilateral chest deformity which started at the level of the sternal angle and arched forward in a manner similar to that described in patients with hyperdynamic pulmonary hypertension. The 2 youngest patients whom we are following have no precordial deformity, and in another patient (Case 9) followed from 2 weeks of age to the present age of 13 years, chest deformity was not appreciated until she was several years old. We think that it is likely that the hugely dilated heart in a young chest with a malleable cage plays the greatest role in producing the deformity. In this regard, it is interesting that the older acyanotic patients of this series and others with smaller, more slowly enlarging hearts have had normal chest contours.

The second finding is a most curious activity appreciated along the left sternal border. This may best be described as a systolic "ripple" or undulatory activity occurring between the second and fourth intercostal spaces 1 to 3 cm. to the left of the sternal border. It is usually associated with only a few low frequency vibrations or no palpable activity. In our experience this finding is peculiar to patients with Ebstein's anomaly. We speculate that this motion results from contraction of the atrialized ventricle either directly or by producing turbulence within the dilated atrium. This wave along with the apical

motion produces, we think, the diffuse activity mentioned by others.[3,4] Finally one frequently discovers a soft thrill when palpating the precordium. Its location varies slightly and may be felt maximally between the xyphoid and apex in the fourth or fifth intercostal space. This thrill probably overlies the tricuspid valve and may be produced by tricuspid insufficiency. As previously noted it does not correlate with the size of the heart[4] and is reported in 55 to 60 per cent of patients.[3, 29] We found no diastolic thrills.

The third finding is a negative one which cannot be overemphasized and which has been referred to by others.[17] It is the absence of either precordial activity from right ventricular enlargement or shock of pulmonary closure. Certainly a cyanotic patient with a malar flush cardiac enlargement precordial bulge undulatory activity along the left sternal border and thrill at the apex, without a right ventricular lift or shock of pulmonary closure can be suspected of having Ebstein's anomaly even before a stethoscope is placed on his chest.

4 AUSCULTATION

a. First Heart Sound The first heart sound was commented upon in 7 of our patients. It was described as increased in 5 and normal in 2 and in none was it decreased The sound was frequently found to have a "clicking" or metallic quality as mentioned by others and often it seemed to be slurred. In 4 patients a sound indistinguishable from an ejection click was heard at the apex. This has been interpreted by others as being due to tricuspid closure delayed by the conduction disturbance that often is present. Previous authors have described the first heart sound as being of decreased or normal intensity.[3,24]

b. Second Heart Sound Closure of the semilunar valves was considered to be of normal intensity in 4 decreased in 8 and increased in 3 patients of this series. Splitting was normal in 6, fine in 8 and not mentioned in the other 3 patients. Widened splitting has been described and thought to be secondary to the conduction disturbance that often is present.[21, 23]

c. Diastolic Sounds After the second heart sound a sound closely simulating an opening snap may be heard.[3] We are uncertain of its origin and think that it may be a delayed closure of the semilunar valves an opening snap of the tricuspid valve, or a sound of ventricular origin similar to the pericardial knock in patients with constrictive pericarditis. Characteristically this sound occurs earlier and is higher pitched than the usual third sound Gallops are frequently described in patients with Ebstein's anomaly.[23] In our series 12 of 14 patients had recognized protodiastolic gallops, and 3 also had presystolic gallops. They are frequently quite loud and may be seen or felt on the chest wall Fig 1 demonstrates the sounds occasionally found in patients with Ebstein's anomaly Here, the first heart sound is delayed and split, with the initial component much less intense than the second and is followed by a high frequency sound which times as an ejection click. After a decreased second heart sound a high frequency sound simulating an opening snap is recorded.

d. Murmurs Patients with Ebstein's anomaly who have no murmurs[3,22,23,30,34] have been described usually in the older age group. In this series 15 patients (88 per cent) had systolic murmur and 8 of these (47 per cent) had diastolic murmurs as well. The systolic murmurs usually exceeded Grade 2 6 and were loudest between the left sternal border and the apex in the third to fifth intercostal spaces. Their quality was usually described as rough or scratchy occasionally harsh or blowing and either plateau or diamond shaped Typically the murmur was long extending nearly throughout the cycle although it occasionally occupied only the first third of systole We noted that the murmur decreased in one case but we usually found it to be either unaffected or slightly increased with inspiration Diastole in these patients is not always easily interpreted. Often the gallop sounds present were of sufficient duration or were summated so that confusion with murmurs occurred In addition as in 3 of our patients there was a to-and-fro murmur of scratchy quality that probably resulted from a friction rub Generally however the diastolic murmurs were low pitched and rather soft. In 3 cases they were early and diamond shaped and in 2 they were

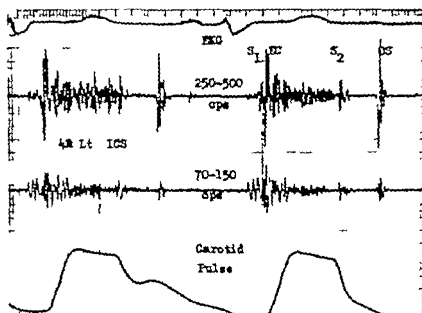


Fig. 1. Ebst[ein's a]nomaly. Phonocardiogram in Case 7 (119365, O. L., age 12 years). See text for comments.

presystolic in timing. There was no appreciable change with respiration. One of the patients without murmurs was 3 days old and the other was 53 years old (Cases 2 and 16).

Various explanations of the origin of the murmurs in this condition have been offered. Those in systole have been thought to arise from an insufficient tricuspid valve, and this must surely be their source in some cases. However, other causes must be sought, since it has been shown that the valve is often competent until late in the patient's course.[21, 22] Other authors have speculated that the systolic sounds arise from blood passing over an enlarged moderator band, from movement of blood over free edges of the valve, or from the turbulence occurring in the "atrialized" right ventricle. *Diastolic murmurs* are thought to result from movement of the valve into the right ventricle during the phase of early filling, or from currents set up in the two proximal chambers.[11] *Since numerous authors have found evidences of tricuspid stenosis, this must be yet another cause.*

F. Electrocardiogram. The electrocardiogram probably contributes more diagnostically in Ebstein's anomaly than in any of the congenital heart lesions. In 75 to 80 per cent of reported cases, a rather characteristic "atypical right bundle branch block" has been found. Approximately 15 per cent of tracings reveal prolongation of the P-R interval, and tall peaked P waves of right atrial enlargement are often found.[4] Voltage of the QRS is usually small in the standard leads, typically less than 10 mm.[14] when R and S waves are combined, compared to a lower normal of 7 mm. In addition, Standard Leads *II* and *III* often reveal a broad R' following a normal R wave that is thought to result from delayed activation of the atrialized right ventricle.[12,14] In precordial leads, a QR pattern with inversion of T waves through Lead V[4] has been thought to be practically pathognomonic of Ebstein's anomaly.[8] The initial forces of the precordial leads are of low amplitude, with the R wave measuring a mean of only 2.6 mm. in Lead V[1], 2.5 mm. in Lead V[2], and 9.9 mm. in Lead V[6].[14] There is often marked splintering of the terminal forces.

Pre-excitation is revealed in the electrocardiograms of about 10 per cent of patients with Ebstein's anomaly.[23] It is always of the B type, resembling a left bundle branch block in the precordial leads with left axis deviation in the standard leads due to a leftward and posteriorly

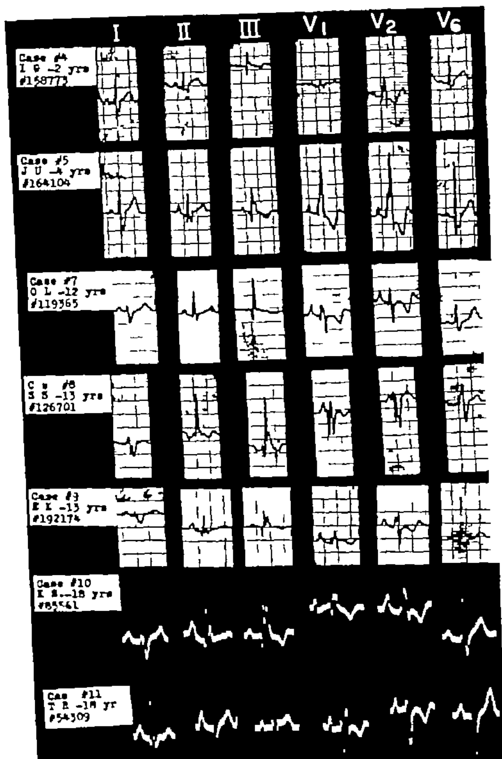


Fig. 2. Electrocardiogram in Ebstein's anomaly. See text for specific comments. Note the similarity of QRS in the majority of tracings. Characteristic is the broad complex with broad, often slurred S in Lead I, R in Lead III, low voltage and terminal S wave in right precordial leads.

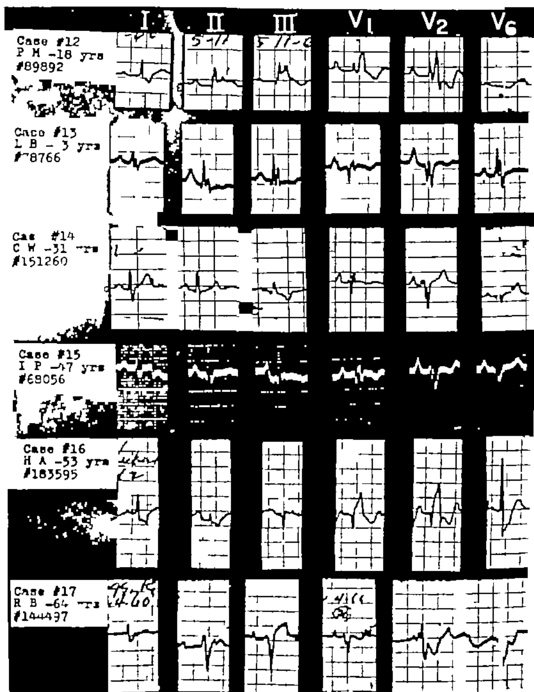


Fig. 3. Electrocardiogram in Ebstein anomaly. See text for specific comments. Note the similarity of QRS in the majority of tracings. Characteristic is the broad complex with a broad, often slurred S in Lead I, R in Lead III, low voltage and terminal S wave in right precordial leads.

Table III. Electrocardiographic findings in patients with Ebstein's anomaly

Case	P amplitude	P-R interval (sec.)	QRS: Duration (sec.)	QRS: Lead I Shape	QRS: Lead I S-wave duration (sec.)	QRS: Lead III (shape)	QRS: Precordial lead (shape) 1	QRS: Precordial lead (shape) 1	QRS: Precordial lead (shape) V	T-wave inversion (lead)
1. M	—	—	—	—	—	—	—	—	—	—
2. L.	—	—	—	—	—	—	—	—	—	—
3. M	—	—	—	—	—	—	—	—	—	—
4. I.G	Normal	0.16	0.09	RSs'	0.06	QRr'	rSR s'	rsR'S	qRS	\
5. J U	Increased	0.14	0.11	RSs	0.08	qRr'	R	rR	qRS	\
6. G.S.	Increased	0.12	0.12	R	None	qS	RS	RS	R	—
7. O.L.	Increased	0.16	0.11	rS	0.08	QR	qRS	qRS	RS	\
8. S.S	Increased	0.22	0.12	rsS	0.06	QRr'	rSR	rsR'S	QRS	V
9. E.K.	Increased	0.16	0.12	rsS	0.08	QRr'	R'S	rrS	qRS	\
10. K.S.	Increased	0.24	0.14	rr'S	0.09	qRR	rSR	rSR	RS	\
11. T R.	Increased	0.18	0.12	qRS	0.08	rSr'	rSr'	rS	QRS	\
12. P.Mc.	Normal	0.24	0.16	RS	0.12	QRR	rsR s'	rsR'S	qR	V
13. L.B.	Increased	0.20	0.14	Rr'S	0.06	qRr	Qrs	rSr'S	Rsr'S	V
14. C.W	Normal	0.18	0.09	RS	0.06	qR	rSR	rS	qRS	\
15. I P	Increased	0.18	0.12	rS	0.08	qR	rsr'	rsr'S'	qRS	\
16. H.A.	Normal	0.18	0.16	rS	0.11	qrR	qrR	qrRs	RS	V
17. R.B	Normal	0.22	0.12	RS	0.08	rS	rsR'S'	R'S	RS	V

directed delta wave vector.[31-33] This is consistent with the concept that type B pre-excitation results from early activation of the septum in the region of the tricuspid valve whereas in type A the early activation is near the pulmonary valve.[31] Occasionally patients have had normal tracings or right axis deviation without conduction disturbance and 2 older patients had left bundle branch block.[20, 27, 28]

Electrocardiograms were available in 14 cases in this series and presented an interesting spectrum (see Figs. 2 and 3 and Table III). P waves were found to be normal in our youngest living patient and in 3 of the older patients. The remainder (70 per cent) had abnormal P waves resulting from an increase in either voltage or duration. The P-R interval was prolonged in 5 cases. In 4 of these it was not secondary to prolongation of the P wave as reported previously,[14] but in one case it appeared to be. The QRS complexes were of normal duration in 2 electrocardiograms, pre-excitation was found in one and left bundle branch block in another.

An intraventricular conduction disturbance of the right bundle type was found in the other 11 cases (77 per cent). Normal conduction occurred in 2 patients (Cases 4 and 14), one 2 years of age and the other 31 years of age, with both having QRS configurations similar to those described below with delayed conduction. One patient when first seen at the age of 2 weeks had a QRS of normal duration, but this had widened by the age of 2 years. Interestingly, the general QRS contour remained unchanged as it increased in duration. The QRS configuration was quite similar in most patients. The majority had right axis deviation of the unblocked forces and the prominent R in Standard Leads II and III. The S wave in Lead I was 0.06 second or greater in all cases. The precordial leads revealed low voltage as described earlier, with most patients having R waves of less than 7 mm. over the right precordium, but in one patient (Case 5) the R in Lead V equaled 16 mm., suggesting right ventricular enlargement. The terminal force was very much

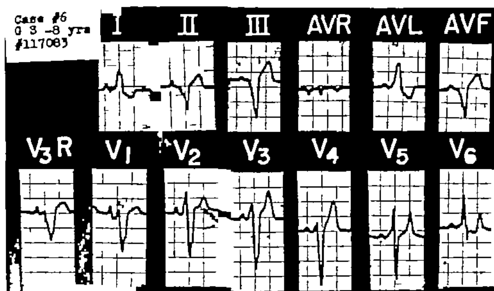


Fig. 4. Electrocardiogram. Ebstein anomaly. Tracing shows pre-excitation of the B type, the delta wave moving leftward superior and posterior direction producing the appearance of left bundle branch block.

anteriorly directed resulting in an S wave rather than an R in Lead V₁ in all and in Lead V₁ in 8 cases. None of the electrocardiograms revealed the QR pattern with inverted T waves through Lead V and only 3 showed low voltage in the standard leads. The electrocardiogram with a type B pre-excitation (Case 6) is shown in Fig. 4. The P-R interval is short and the QRS is widened by the delta wave which is directed leftward superiorly and posteriorly. This tracing is very similar to those seen previously in patients with Ebstein's anomaly. It is noteworthy that this patient who died in congestive heart failure at the age of 8 years had no history of tachycardia.

Patients with Ebstein's anomaly have very similar electrocardiograms, as can be seen by comparing the findings shown in Table III. The majority have QRS prolongation due to the delayed conduction through the right bundle. This bundle branch block is atypical because of low voltage in all leads and the marked anterior direction of the blocked forces resulting in a terminal S wave instead of the R in Leads V₁ and V that characterized the typical right bundle branch block. We wish to emphasize the peculiar R that is frequently seen in Standard Leads II and III but urge caution in considering this as being "specific" for Ebstein's anomaly. For example, the electrocardiogram in Fig. 5 was from a patient with a surgically proved atrial septal defect who had such an R and a tracing quite similar to that of Case 5 with Ebstein's anomaly (Fig. 2).

The conduction disturbance described usually exists when the patient is first seen. However, in numerous cases, including one in this series (Case 9), an initially normal tracing evolved into the typical one during follow-up. In some cases, abnormalities of conduction are seen only during arrhythmias. In this regard we wish to call attention to the electrocardiograms obtained in Case 17 (Fig. 6). This 64-year-old patient, during a bout of atrial tachycardia, had on a continuous tracing complexes alternating between normal conduction, atypical right bundle branch block, and left bundle branch block. Between bouts of arrhythmia he had either normal conduction or left bundle branch block (Fig. 7). We have been unable to correlate electrocardiographic changes with a patient's clinical course. Others have stated that the progressive increase in the voltage of the T wave may be associated with clinical deterioration.

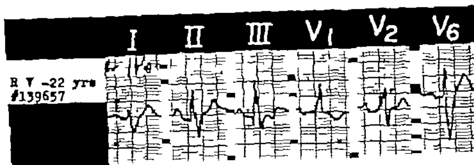


Fig. 5. ECG resembling that in Ebstein's anomaly in patient with surgically proved atrial septal defect with normal tricuspid valve. Comparison with the tracing of Case 5 in Fig. 2 reveals striking similarity.

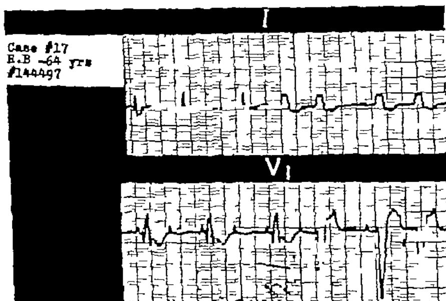


Fig. 4. Electrocardiogram in Ebstein's anomaly. Continuous (not simultaneous) strip of Lead I and V1. Note: In Lead I complex number *one* resembles that of right bundle branch block, complexes 2 and 3 normal conduction, and the remaining ones are those of left bundle branch block. Lead V1 shows typical Ebstein complexes in the first three complexes; the remaining ones are those of left bundle branch block. An atrial arrhythmia and A-V dissociation are also present.

This has not been our experience and in fact, several of our patients with clearly abnormal P waves continue to enjoy relatively normal exercise tolerance. Type B pre-excitation should always suggest the diagnosis of Ebstein's anomaly in the cyanotic patients. Unfortunately this conduction disturbance is not peculiar to Ebstein's anomaly and has been seen in patients with tetralogy of Fallot, tricuspid atresia, and transposition of the great vessels.[4]

Explanations have been offered to account for the electrocardiographic changes. The blocked right bundle has been thought to result from pressure produced by the enlarged right atrium on the upper part of the right septal surface.[11] The small voltage has been considered to be the result of thinness of the right ventricle and a decreased number of fibers in the atrialized right ventricle as compared to voltage created by a normal left ventricle.[14] We have wondered why voltage is low

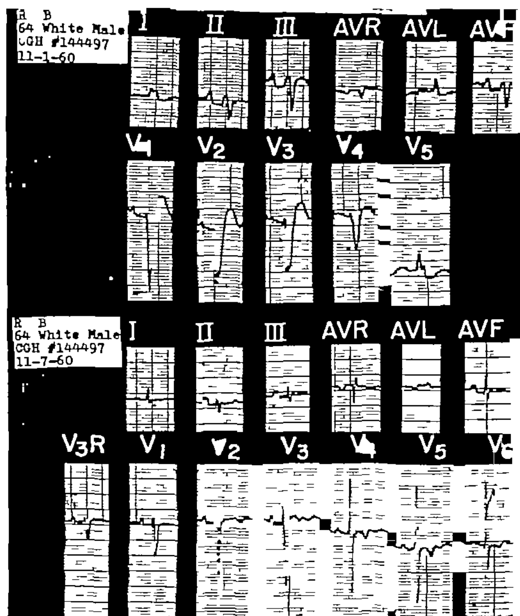


Fig. 7. Ebstein anomaly. Electrocardiograms taken during the terminal admission of Case 17. Upper tracing demonstrates a left bundle branch block, whereas the lower one reveals normal conduction in the 64-year-old patient.

since in other situations in which dilated chambers occur *without hypertrophy of muscle* as with acute right strain voltage is often greatly increased. A few patients with Ebstein's anomaly have in fact shown voltage sufficient to suggest right ventricular enlargement.[8,47] Case 4 in this series with R voltage of 16 mm in Lead V1 would fall into this small group.

G. X-ray findings. The characteristic x-ray film in Ebstein's anomaly reveals several salient features including normal to decreased lung markings depending on the amount of right-to-left shunting, a narrow pedicle due to an inconspicuous aorta, and a globular or box-shaped cardiac silhouette. It has been shown that the appearance of the cardiac silhouette is secondary to the right atrium or its effect

on adjacent structures. Films made post mortem of hearts filled with contrast medium have revealed that practically the entire cardiac shadow is right atrium save for a small amount of right ventricle seen along the lowermost left margin.[33-35] The infundibulum, often dilated and/or hypertrophied, is displaced superiorly and may produce a shelf-like appearance to the uppermost portion of the left silhouette and obscure the main pulmonary artery.[1, 34] Oblique views of the chest demonstrate both filling in of the retrosternal space and overlapping of the spine, thus suggesting biventricular enlargement. Again it has been shown that the huge right atrium is responsible for this appearance.[34, 35]

Cardiac fluoroscopy, thought by some to be important, has been described as revealing a decreased amplitude of pulsation in the aorta, pulmonary vessels, and heart shadow.[33] Others have pointed out that decreased activity is seen only late in the patient's course and that earlier a contraction of the right atrium occurs which produces a sudden sharp motion. The proximal portion of the right ventricle is quiet, whereas the distal portion of the chamber may be very active. The usefulness of the angiocardiogram varies with the author. Some think that the injection into the huge right atrium offers little help,[27] whereas others think that the "hanging up" of medium in the atrium instead of the ventricle, as seen in most conditions, is helpful.[34] Other observations which are described include the evidence of right-to-left shunting, decreased opacification of the pulmonary artery, and, perhaps most important, a peculiar deep notch on the inferior border of the silhouette far toward the right. This has been thought to be a "pathognomonic" sign and to represent the separation of the proximal portion from the distal portion of the right ventricle by a ridge of muscle at the caudal line of the fusion of the valve leaflets separating the right atrium and right ventricle.[33, 34, 41]

X-ray findings in this series of patients add little to the previous discussion (Table IV). All of our patients had some cardiac enlargement (see Figs. 8 and 9), and the degree of enlargement correlated fairly well with the severity of symptoms. All patients were able to pursue essentially normal activities while heart size remained at +2 or less, except Cases 16 and 17, who complained of severe physical limitation with only slight cardiac enlargement.

Table IV. X-ray findings in patients with Ebstein's anomaly

Case	RA	RV	LA	LV	Heart size	Pedicle	Aorta	MPA	Lung marking
1. M.	—	—	—	—	—	—	—	—	—
2. L.	—	—	—	—	—	—	—	—	—
3. M.	—	—	—	—	+3	—	N	—	—
4. I.G.	N	N	N	—	+1	Normal	N	N	N
5. J.U.	+3	+	N	N	+2	Normal	N	↓	N
6. G.S.	+1	N	N	N	+3	Narrow	↓	↓	
7. O.L.	+2	+Out	N	N	+1	Narrow	↓	N	
8. S.S.	+4	+	N	±	+4	Narrow	↓		
9. E.K.	+4	+	N	N	+2	Narrow			N
10. K.S.	+3	N	N	N	+4	Narrow	↓	↓	
11. T.R.	+1	+Out	N	N	+2	Narrow		↓	↓
12. P.Mc.	+3	+	N	+	+2	Normal		N	N
13. L.B.	+4	+	N	±	+4	Narrow		↓	↓
14. C.W.	+2	N	N	+	+2	Normal	↓	↑	N
15. J.P.	+3	+	N	+	+3	Normal	↓	N	N
16. H.A.	+1	N	N	+	+1	Normal	N	↑	N
17. R.B.	N	N	N	+	+1	Normal	N	N	N

RA, Right atrium. RV, Right ventricle. LA, Left atrium. LV, Left ventricle. MPA, Main pulmonary artery. N, Normal.

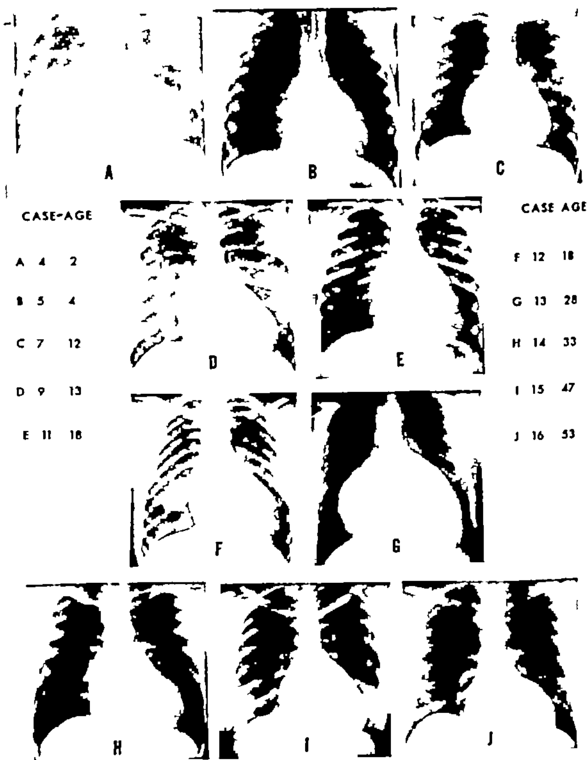


Fig. 8. Posteroanterior films of patients in this series who are still living. Case numbers and ages are listed. See text for comments.



Fig. 9 Posteroanterior films 1 3 of the patients with Ebstein anomaly who died. A Case 6, age 8 years. B Case 8 age 13 years. C Case 17 age 64 years.

The symptom in these older patients was dyspnea which was thought to be secondary to bouts of tachycardia.

We have been impressed that the general configuration of the heart remains quite similar during follow-up with progressive enlargement being the only change seen as symptoms increase

The only constant feature of the x ray films as can be seen is right atrial enlargement producing a sweeping convexity of the right cardiac border This contour is perhaps more gradual than the shelf-like projection from right atrial enlargement in most conditions. None of our patients has had evidence of left atrial enlargement.

As pointed out by others, it is common for the x-ray films to suggest left ventricular enlargement. This is seen especially in Cases F H I and J of Fig 8 and in Case C of Fig 9

The pulmonary markings were considered to be normal in of our patients and decreased in the other 6, and were inversely related to the degree of cyanosis. The main pulmonary artery was often obscured in the patients with globular hearts was inconspicuous in several but was considered to be prominent in Cases H and J of Fig 8

No patient had a prominent aorta. The typical x-ray finding while often noted especially late in the course of the young and middle aged patients is by no means constant and early diagnosis will be missed in the majority of patients if it is considered to be a requisite [36] It is true that the enlarged right atrium produces a sweeping convexity of the right heart border in practically all cases and leads to cardiac enlargement of some degree in the vast majority [3]

H Cardiac catheterization Numerous benefits are to be derived from catheterization in the patient with Ebstein's anomaly even though the procedure is not without its dangers. It has been generally agreed that, although risks are involved in the performance of such diagnostic procedures they were probably overemphasized in the older literature and with proper caution the difficulties are usually avoided [22,29] As noted however several sudden deaths have occurred during or shortly after catheterization or angiocardiography [41] In addition arrhythmias are commonly encountered and may be related to the fatalities.

The catheter enters the large right atrium and usually coils. In 20 to 25 per cent of cases it crosses the atrial defect and enters the left atrium Generally it can be got into the right ventricle often after some difficulty but in 25 to 30 per cent it cannot be made to enter the pulmonary artery

Of considerable importance is the location at which ventricular pressure occurs that is where the tricuspid valve is located Frequently it is found to be several centimeters to the left of the spine in the anteroposterior projection and occasionally nearly against the left cardiac border high up the silhouette [8,36] In cases in which the valve overlies the spine its malposition

is best appreciated in lateral films and is found to be inferior and more anterior than normal.[25] Pressure in the right atrium is usually slightly elevated,[4] although a large atrium may have normal pressure. The tracings often reveal a prominent "A" wave that is thought to *reflect the atrial hypertrophy resulting from impedance of forward flow.* This is said to be more pronounced if no atrial defect exists.[4, 8] A prominent deflection termed an "S" wave is frequently seen which precedes the "V" wave and interrupts the "C" wave.[41] This may result *from insufficiency of the tricuspid valve* or may simply reflect the pressure produced by the blood being pushed into the atrium when the "atrialized ventricle" lying above the valve contracts. Obviously, then, it may be difficult to confirm the presence or absence of tricuspid insufficiency. Tricuspid stenosis has been found in several patients, and many patients[4, 12, 23, 77] have been thought to have insufficiency of the valve.[29, 77]

Right ventricular systolic pressure is usually normal and thus is of considerable diagnostic significance in the cyanotic patient. The end-diastolic pressure is often high from the effects of atrial contraction[20, 36] or perhaps from overfilling of a small right ventricle even before atrial contraction occurs, thus resembling the "restriction" seen in patients with constrictive pericarditis.[73]

Several patients have shown elevated pressures in the right ventricle, with the majority of these demonstrating a gradient, although usually a small one, across the outflow tract.[17, 23, 77] This gradient has been thought to be secondary to hypoplasia of the pulmonary ring, since infundibular or valvular stenosis in the condition is rare.[17, 23, 77] Recordings of pressure in the pulmonary artery have varied and often have shown a wave synchronous with atrial contraction, leading to speculation that the atrium functions as an accessory ventricle.[4, 8, 23] Several patients have had elevated pulmonary arterial pressures.[2]

Systemic desaturation is present in 85 to 90 per cent of cases, although this is seldom marked and often requires exercise to demonstrate. Evidence of left-to-right shunting has been seen in as many as 25 per cent of patients.[2, 3, 73] At least 2 have manifested cyanosis but did not have a septal defect at autopsy.[3] The use of an intracavitary electrode to demonstrate the location of the tricuspid valve has been shown to be useful in establishing the diagnosis of Ebstein's anomaly.[41, 50, 51] On pull-back *from the right ventricle, the finding* of a fall in pressure below that recorded in the atrium, with persistence of the monophasic ventricular wave on the electrode tracing, is considered to be pathognomonic of the presence of an "atrialized ventricle."[41] In a series of 300 normal subjects, *this never occurred*[50]; *however, other authors* have described false-positive and false-negative results.[73, 80] Of greater significance is the finding of ventricular extrasystoles and an S-T segment current of injury when the catheter is pressed against the wall of the atrialized ventricle. Neither would be expected with stimulation of an atrial wall; however, again misleading results may be obtained.[80]

Catheterization was performed in 9 of our patients, and the results are shown in Table V. No fatalities or serious consequences were encountered, although 2 patients developed atrial arrhythmias that reverted without sequelae. The catheter entered the pulmonary artery in only 6 patients, and crossed into the left atrium in 2. Pressures were elevated in the right atrium in 7. Right ventricular systolic pressures were upper normal in 3 patients and clearly elevated in one patient. In 5 the right ventricular end-diastolic pressure exceeded 5 mm. Hg. A gradient of 3 to 7 mm. occurred across the outflow tract in all patients. In one, a gradient was recorded between the right atrium and right ventricle. In 6 patients the valve was noted to be located several centimeters to the left of the midline. Five patients had arterial desaturation, but of greater interest was the fact that 4 were not desaturated even though 2 of these patients subsequently became clearly cyanotic (Cases 9 and 13) later in their course. In no case was a left-to-right shunt appreciated. Cardiac output was reduced in 3 patients.

I. Course. The total number of reported patients includes fewer than 100 who had died, and few of those still living have been followed for more than 10 years. Therefore

Table V Cardiac catheterization findings in patients with Ebstein s anomaly

Case	Age (yr)	Pressures (mm Hg)			Saturation (vol. %)						Systemic index	Pulmonary index	Shunt (L./min.)	Comment
		RA	RV	PA	IVC	SVC	RA	RV	PA	BA				
3 J U	2	6/3	45/0/7	—	—	—	37	36	—	73	3 9	[illegible]	—	N PA, valve to left of spine. Catheter passed through a patent foramen ovale
6. G S.	5	A 10/5	30/0/7	—	71	61	68	68	—	84	4 4	3 1	1 3	N PA. Catheter passed through patent foramen ovale—Mild gradient
9 E h.	5	A 7/6	23/0/4	19/9	—	55	61	61	—	91	4 1	4 1	0	Valve t left of spine. N shunt with exercise. Mild gradient
10. h.S.	18	12/4	20/3	17/9	48	50	54	54	33	79	1 4	3 0	0 8	—
11 T R.	8	A 12/5	24/4/11	20/9	39	38	61	—	69	77	3 9	1 9	2 0	Valve to left of spine. Developed PAT (R 180)—Mild gradient
12 P M	—	4/1	17/0	15/1	—	36	62	63	71	86	—	—	—	—
13 L B	21	A 10/4	29/3/13	22/10	70	55	60	61	62	95	3 0	3 0	0	Mild gradient t outflow tract. Atrial fibrillation during catheterization, valve to left, right-to-left shunt with exercise (0.5 L./min /M 2)
14 C R	31	A 10/2	22/0	—	—	63	63	61	—	94	2 0	3 0	0	Valve t left of spine. N PA
15 J P	39	A 10/3	29/0/9	22/9	—	—	—	—	72	96	1 9	1 9	0	5 mm. gradient between RA and RV right-to-left shunt with exercise (0 7 L./min./M 2)

RA Right atrium. RV Right ventricle PA Pulmonary artery IVC Inferior vena cava. SVC Superior vena cava. BA Brachial artery PAT Paroxysmal atrial tachycardia. A A wave.

the natural history of the disease is as yet uncertain and the course to be expected in an individual case should be approached with an open mind. As noted previously, the majority of patients describe easy fatigability and dyspnea on exertion from early childhood, with cyanosis generally appearing before their teens. It is to be re-emphasized that this varies greatly, that patients may have no symptoms until adulthood and that cyanosis may never develop. With the onset of symptoms, we note once again a broad spectrum. Typically, there is gradual but progressive deterioration; however, some patients remain stable for prolonged periods, as with our Case 17, who changed little in 30 years. Paroxysmal bouts of tachycardia may begin at any age and seem to be of little prognostic significance except that older patients often tolerate them poorly.[12] The development of congestive failure would seem to be a grave prognostic sign and generally is seen only late in the course, although patients have survived for as long as 0 years after failure began.[21]

We have been impressed by the fact that, when the patient with Ebstein's anomaly begins to deteriorate, marked changes in the physical findings frequently occur. The precordial activity decreases, the pseudo-thrill may disappear, and murmurs may change in intensity, quality, and timing. For example, Case 13 of this series presently has only a short, rather soft, nondescript systolic murmur remaining, with the scratchy systolic and diastolic murmurs having disappeared after a fixed atrial fibrillation and congestive heart failure developed. Conversely, in Case 8, a to-and-fro scratchy murmur became much louder a few days before death.

It appears, therefore, that the findings may depend upon the time in the course when a patient is seen: if very early, the findings may be minimal or absent and yet become typical with the passage of time; if only late, it is quite conceivable that they may be nondiagnostic if not misleading, and diagnosis becomes even more difficult. Changes in physical findings may result from alteration in hemodynamics produced by various developments such as dilation of chambers, fall in cardiac output, or onset of arrhythmias.

The average age at death has been 23 to 26 years[3,10,13,22] and the life expectancy at birth is approximately 35 years.[22] Congestive heart failure has been associated with or has been the cause of death in approximately one third of the cases,[3,24] which exceeds only slightly the 20 per cent incidence of sudden deaths.[3,19,20,21,24] The next most common cause of death (in approximately 20 per cent of cases) and one which should give us much concern is diagnostic procedures or surgery.[3,4,24] Also of significance as a cause of death, but affecting considerably fewer patients, are cerebral abscesses or paradoxical emboli. The latter have been reported most frequently in the older patients and have accounted for 25 per cent of the deaths in those over 50 years of age. Brain abscess has been seen in 4 patients, and only one patient (Case 13) survived.[12,13,22,24]

Interestingly, bacterial endocarditis has never been reported in a patient with Ebstein's anomaly. Other infections have caused death in patients with Ebstein's anomaly, with tuberculosis being most frequently mentioned[3] and thought to be associated with the decreased pulmonary blood flow. Case 12 of our series had this complication but responded well to medical management.

It has been said that the size of the distal portion of the right ventricle is the single most important factor that decides how a patient with Ebstein's anomaly will fare. If it is small, the patient has severe symptoms and dies early, and if it is of normal size, he may do well.[13,31] It has also been observed that the age at the time of onset of cyanosis is inversely related to the prognosis. If desaturation is noted in infancy, the average age at the time of death is 12 years, compared to survival for much longer periods if cyanosis appears later.[19]

Pathologic findings

Six patients in this series died and all were autopsied (Cases 1, 2, 3, 6, 8, 17). The cardiac anomaly was thought to have contributed to death in each case except in the 3-day-old infant who died of respiratory-distress syndrome and birth

trauma. The heart with Ebstein's malformation is usually heavy although not to the degree anticipated from its size since the enlargement is primarily atrial rather than ventricular. It was found to be two to three times the normal weight in 5 of our 6 cases being normal only in the neonate who died of other causes.

As noted earlier the finding of fibrinous pericarditis overlying the right atrium has been recorded and it was found in 2 of our patients associated in one with 400 ml. of sanguineous pericardial effusion.[22,41] The speculation has been that these findings result from extravasation of blood from the coronary veins subjected to increased pressure.[42] One must doubt this explanation since other conditions with high atrial pressures, such as tricuspid or pulmonary atresia or stenosis, are not associated with pericarditis or effusions.

The great vessels are usually normal in size and location and were found to be so in our cases. The pulmonary artery may be small although proportionate usually to the size of the distal right ventricle. However in 2 patients living to ages 14 and 34 years, it was reported to be hypoplastic.[36] Hypoplasia and coarctation of the aorta have been reported.

Intracardiac lesions other than those comprising the anomaly are uncommon. Several patients have had small ventricular septal defects usually entering the atrialized right ventricle above the level of the tricuspid valve[7,43] as was found in one of our cases (Case 1). One patient was thought to have an endocardial cushion defect, with a resulting A-V canal[38] and others have had infundibular or pulmonary valve stenosis.[11,21,47]

The left side of the heart is normal in the majority of cases. Patients with corrected transposition of the great vessels frequently may have deformity of the A-V valve with resultant left-sided Ebstein's.[11,45,53,56,57]

The left ventricle is occasionally found to be dilated, hypertrophied, or fibrotic. This may be seen in the young but more often in older patients[21,17,56,44,47,34] in whom systemic hypertension or coronary artery disease may be responsible. In our material left ventricular hypertrophy was found in the 64-year-old patient with a history of systemic hypertension and for no apparent cause in a 13-year-old boy. It is conceivable that these changes result from prolonged diastolic overloading of the left ventricle due to right-to-left shunting. The mitral valve has been found to be thickened[17,37,41,47] or nodular and in one patient it was deformed by a thick bar of tissue across the commissure openings resulting in rigid leaflets and mitral stenosis.[39] One case with supravalvular stenosis is recorded.[71]

All parts of the right heart are affected by this anomaly. The right ventricle is divided by the abnormally positioned tricuspid valve into a proximal or "atrialized" portion and a distal portion. The size of each varies considerably from patient to patient and it is thought that the capacity of the distal portion of the right ventricle to a great extent decides the clinical course. If it is nearly normal in size the patient often does quite well. Typically it is reduced in volume with hypertrophy of the wall. The moderator band may be prominent and it is possible that this accounts for the pressure gradient across the outflow tract that is noted so frequently. The proximal portion of the right ventricle is usually quite thin walled and some authors have thought that this is not the result of dilation alone but a significant part of the inherent defect.[14] The finding of hypertrophy of that portion of the right ventricle as recorded before and seen in one of our patients (Case 8) casts some doubt on this theory.[22] In this series, the distal portion of the right ventricle was small in all except Case 2. In the 64-year-old patient it consisted of no more than an outflow tract, with all the remaining ventricle being "atrialized." The proximal or atrialized ventricle varied in size and thickness. In Case 2 it was a small chamber (valve only 2 mm. below ring) of normal thickness. In the other patients it was much larger and often of greater volume than the distal portion. The wall was usually thinned to 1 to 3 mm. however in Case 8 it was equal in thickness to the distal chamber and both measured 4 mm. The right atrium was hypertrophied and hugely dilated comprising most of the heart in all cases.

Right atrial dilation often massive is

a constant finding. The wall is usually hypertrophied and adherent thrombi are not rare. The Eustachian and Thebesian valves are frequently prominent and it has been proposed that these serve to protect the inferior vena cava and coronary sinus respectively from the effects of high right atrial pressure.[22,23,27,64]

Although approximately 5 to 10 per cent of the patients have the atrial septum intact, the remainder have a defect.[4] In the vast majority this is a patent foramen ovale, but secundum type defects may occur[48,7] either alone or with a patent foramen ovale. All of our cases had a widely patent foramen ovale, including the acyanotic Case 17.

The structure of the tricuspid valve varies considerably. In all there is depression of portions of the valve into the ventricle because these (1) arise from below the true A-V ring, (2) arise from the true A-V ring but have valve tissue adherent to the ventricular wall, or (3) arise from the A-V ring and are essentially free from the wall but have shortened chordae tendineae and papillary muscles that cause the valve to lie adjacent to the ventricular wall.

In the majority of patients the anterior leaflet arises totally or in part from the A-V ring, whereas the septal one may or may not do so and the posterior leaflet usually arises below the ring and is the most deformed, often being no more than a wrinkled vestigial structure plastered to the ventricular wall. The area of ventricle situated above the origin of these leaflets comprises the "atrialized" ventricle and varies considerably in size depending on the depths within the ventricle at which the septal and posterior leaflets arise, which may be nearly at the apex.

In some patients all leaflets arise below the true A-V ring, and less often all arise from the ring, but because of abnormal fusion of the leaflets to each other or to the ventricular wall an "atrialized" ventricle results. In such cases the valve consists of the remaining leaf or leaflets fused to form a large curtain. When this occurs the blood passes through fenestrations in the curtain or through holes present between the lateral margin of the leaflet and the free ventricular wall.[31,33] Commonly all three leaflets are identifiable and fused with each other to form varying shapes, with the anterior leaflet usually being largest and contributing most to the valve.

The valve tissue varies in consistency and may be thick, thin, smooth, or nodular. Often one or more leaflets may be no more than a shrunken thick mass firmly adherent to the ventricular wall and hardly identifiable. The papillary muscles and chordae tendineae occasionally are all well developed, but usually those supplying one or more of the leaflets are quite underdeveloped and seemingly[4,23,31,35,38,40] functionless.

It has been proposed that the characteristics of the valve are dependent upon the stage during fetal development at which a disturbance occurs; if early, all portions of the valve arise from the ventricle, and if late, the leaflets arise from the true A-V ring but the valve substance is adherent to the ventricular wall.[15]

Discussion

Attempts to explain the tricuspid anomaly embryologically have been unsatisfactory. Perhaps this results from our poor understanding of the development of the valve tissue.[40,44,66]

The theories advanced to explain the origin of the lesion have been several, with those that seem to be most reasonable considering it to be an abnormality that occurs in the 15- to 20-mm. embryonic phase.[40,43,44]

The hemodynamic alterations that result from the structural abnormalities can be understood reasonably well. Contraction of the dilated atrium usually is effective in propelling blood into the ventricle; however, the proximal portion of the ventricular chamber distends and reduces the amount of blood reaching the distal portion. The atrium probably does not empty completely and some blood may cross the foramen ovale, which acts as an escape valve.[23]

In the majority of cases, the tricuspid valve is reasonably competent. Occasionally a patient has mild stenosis and more often varying degrees of insufficiency are observed. Some authors have thought that the stenosis which is present in early life gives way to a competent valve without

obstruction in childhood and later to insufficiency as the A-V ring dilates progressively[44, 46] and the valve becomes thickened. That insufficiency should occur seems to be inevitable because of the presence of fenestrations, inadequate length of leaflets, shortened chordae and poorly developed papillary muscles.

With ventricular contraction blood from the distal chamber is ejected into the lungs and since this volume is small reduced pulmonary flow results. The contents of the atrialized ventricle cannot be propelled forward since the valve distal to it is closed and the distal chamber is unable to accept additional blood because of its reduced size. Retrograde flow results, with the blood either remaining to distend further the right atrium or crossing the patent foramen ovale to produce cyanosis.

The symptoms of weakness, dyspnea, and ease of fatigability are probably the result of a decreased cardiac output. Paroxysmal arrhythmias are also frequent and presumably result from irritable foci developing in the dilated atrium.

The physical findings and their origins have been discussed in detail earlier as have the laboratory findings.

Life is shortened in the majority of patients with Ebstein's anomaly and death is usually related to the hemodynamic alterations resulting from the anomaly or to complications such as paradoxical emboli or brain abscess, which are made possible by it. Sudden death presumably the consequence of arrhythmias, is common. Although undocumented it seems to be likely that these arrhythmias may be ventricular in origin arising in the thinned and dilated atrialized ventricle. That atrial arrhythmias do cause death in this group is certain however and is demonstrated by Case 17 of this series.

The complications seen and the course to be expected differ strikingly in different age groups. Table VI lists 30 patients from the literature who died at or before 10 years of age. Several generalizations seem to be justified concerning the young patient with Ebstein's anomaly. (1) Although the tricuspid valve deformity may be severe enough to cause early death survival during infancy and early childhood is the rule if intrauterine survival has occurred. (2) One of the early signs of deterioration is congestive heart failure but this may precede death by several years and many initially respond to medical management. (3) Sudden death is uncommon in this age group. (4) Nearly 50 per cent of the reported deaths in patients under the age of 10 years have followed diagnostic procedures or thoracotomy. Obviously some of these patients were severely ill prior to the procedure. (5) Since the outlook for survival is good sudden death is uncommon and surgical procedures are associated with a high mortality it seems to be reasonable that extensive diagnostic procedures which may be poorly tolerated should be avoided if the diagnosis can be established on clinical grounds.

In contrast to the usual patient, individuals over 50 years of age who have Ebstein's anomaly present quite a different picture (Table VII). They have generally enjoyed good health pursued active lives, raised large families or tolerated physically demanding jobs. Some patients have had bothersome although not disabling dyspnea on exertion or paroxysms of atrial tachycardia. Since cyanosis and murmurs are present in only about 50 per cent of these patients, and the latter are frequently systolic and nonspecific one cannot rely on the presence of typical features to suggest the diagnosis. The cardiac silhouette on the x-ray film is often nondescript and has appeared to be normal or nearly so in some cases. The electrocardiogram is probably the most helpful tool in the diagnosis of Ebstein's anomaly and yet the "typical" form of right bundle branch block was found in less than half of the older patients. The finding of left bundle branch block in 25 per cent of the group is notable and one patient (Case 17) alternated between left bundle branch block right bundle branch block, and normal conduction. The mode of death in these patients differs significantly from that in younger ones also. The majority of those with defects in the atrial septa (patent foramen ovale or atrial septal defects) had at autopsy widespread emboli presumably paradoxical. This is seldom seen in the younger patient with Ebstein's anomaly. In the

Table VI Findings in patients with Ebstein's anomaly who died under 10 years of age

Case	*Reference*	*Age*	*Sex*	*Cyanosis*	*Murmurs*	*CHF*	*Catheterization*	*Surgery*	*Death*
1	Present	Stillborn	F	—	—	+	—	—	CHF
2	3	Stillborn	?	—	—	—	—	—	Prolapsed cord
3	4	26 hr		+	+	+	—	—	CHF
4	8	2½ day	?		?	?	?	?	Possibly not dead
5	Present	3 day	F	+	0	0	0	0	Respiratory-distress syndrome
6	Present	4 day	F	+	+	+	0	0	CHF
7	3	9 day	?	?	?	+	0	0	Hypoplastic aorta
8	5	10 day	F	+	+	?	+	Thoracotomy	At surgery
9	7	2 ½ mo	?	?	+	?	0	0	Corrected transposition and VSD
10	7	2 mo		?	?	?	?	?	N details
11	6	8 mo	F	+	0	+	0	0	URI
12	5	16 mo	F	+	+	?	0	Potts Smith	12th postop. day
13	9	2 y	M	+	+	0	+	AP window	2nd postop. day
14	10	2	M	0	+	0	+	0	At catheterization
15	3	2 y	?	+	?	+	+	0	After angiocardiography
16.	11	3 y	F	+	+	0	0	—	2° Measles and bronchopneumonia
17	12	3 y	F	+	+	+	+	Infundibulectomy nd VSD closure	At surgery
18	13	4 yr	F	?	?	?	?	?	No detail
19	14	4 ½ yr	F	+	+	0	0	0	Sudden death
20	15	5 y	M	+	+	?	+	Blalock Taussig	At surgery
21	16	6 y	M	+	+	0	+	Thoracotomy	Induction of anesthesia
22	Present	6 y	F	+	+	+	+	0	CHF
23	17	7 y	F	+	?	?	?	?	N tural death
24	18	8 yr	F	?	?	?	?	Thoracotomy	At surgery
25	3	8 yr	?	+	—	+	+	0	At catheterization
26.	19	9 y	?	?	?	?	+	0	After angiocardiography
27	14	10 yr	F	+	+	+	0	0	Sudden death
28.	11	10 r	F	+	+	0	0	0	Brain abscess
29	20	10 yr	F	+	+	0	+	Closure PFO	Postop. cerebral infarct
30	67	10 y	F	+	+	+	?	+	Induction of anesthesia

CHF Congestive heart failure *PFO* Patent foramen ovale *AP window* Aorticopulmonary window *URI* Upper respiratory infection. *2° measles* Secondary to measles 0 Absent or none. ? Unknown.

remainder of the cases death was the result of uncontrollable atrial tachycardia or was due to causes that were seemingly unrelated to the cardiac anomaly In this group as with the very young sudden death is uncommon Congestive heart failure when it occurred was usually noted very *late in the patient's course* and this may be of prognostic significance

Therapy in patients with Ebstein's anomaly is frustrating We are unaware of any means available to prevent the sudden death or progressive deterioration When failure does occur the initial response to digitalis and diuretics may be good but the relentless course continues in the majority The surgical approaches to date have been less than satisfactory By far the majority of patients who have *been operated upon* have died at the time of operation or shortly thereafter Several of the deaths occurred for unknown reasons during the induction of anesthesia [1, 36, 47] or after thoracotomy or ventri

Table VII Findings in patients over 50 years of age with Ebstein's anomaly

Case	Reference	Year	Age (yr)	Sex	Cyanosis	Murmur	Symptom	CHF	ECG	X-ray	Cause of death
1	21	1936	51	F	+	+	PAT 14 yr	0	2° A V RAD RBBB	CE	Tachycardia
2.	2	1918	51	F	+	0	1 y	+1 y	RAD	CE	Pulmonary infarct and paradoxical emboli
3	Present	1966	53	M	+	0	DOE y	0	RBBB	CE	Living
4	3	1954	55	F	0	+	0	0	LAD RBBB	0	Cerebral infarcts, pulmonary infarct
5	24	1960	60	M	?	+	Seizures	0	RBBB WPW	CE	Paradoxical embolism mesenteric thrombosis
6.	5	1886	60	F	0	0	?	0	—	0	After cataract surgery
7	26	1903	60	M	?	+	2 y	+	—	0	Paradoxical emboli spleen kidney brain
8.	27	1955	63	M	+	+	CHF 20 y	+20 y	AF RBBB	CE	CHF CVA (not embolic)
9	Present	1963	61	M	0	+	PAT 60 y	+	Normal RBBB LBBB	CE	Tachycardia
10.	46	1951	72	M	0	0	PAT 10 y	0	LBBB	0	Tachycardia
11	48	1960	75	M	0	0	Dyspnea 25 yr	0	AF	Normal	Bladder tumor after induction of caudal anesthesia
12	47	1956	79	F	+	0	0	0	1° A V LBBB	0	2° Obstructive jaundice
13	93	1966	79	F	0	+	Dyspnea and CHF 12 y	+	AF RBBB	CE	Congestive heart failure myocarditis

1° and 2° A V: First and secondary atrioventricular block, respectively. PAT: Paroxysmal atrial tachycardia. DOE: Dyspnea on exertion. CHF: Congestive heart failure. CE: Cardiac enlargement. CVA: Cerebral vascular accident. 2° Obstructive jaundice: Secondary to obstructive jaundice.

culotomy without other manipulation.[4,17,48] The majority of patients undergoing shunting procedures, usually prompted by an incorrect diagnosis, died.[6,9,15,24] It is reasonable that the right ventricle is unable to adjust to an additional burden imposed upon it by greater quantities of blood entering the pulmonary circulation, as has been pointed out previously.[14]

In recent years at least three surgical approaches have been proposed to beneficially affect the altered hemodynamics. One which has met with little success involves elevation of the displaced leaflets to the true annulus by a plicating procedure designed to exclude the atrialized ventricle and narrow the A-V ring.[47] The operation most widely accepted to date is that of anastomosing the superior vena cava to a pulmonary artery. This was first proposed in 1954 as a means of increasing pulmonary blood flow and reducing the atrial blood flow, thus lowering atrial pressure, reducing right-to-left shunting, and decreasing the irritability of the atrium that results in arrhythmias. The first successful application of this procedure was reported in 1959[48] and numerous subsequent cases have appeared.[4,7,73,83]

The most exciting approach has only recently been reported. Several patients *have had successful replacement of the* deformed value by some type of prosthetic valve with beneficial result.[73,8] Only time will permit critical evaluation of this procedure, but if practical it will permit us to approach the patient with Ebstein's anomaly with optimism for the first time.

Summary

Seventeen cases of Ebstein's anomaly have been presented; the diagnosis was confirmed by autopsy in 6 and made on clinical grounds in the other 11. The series includes the youngest patient dying of the lesion, a stillborn infant, and the fifth oldest patient thus far reported (64 years).

The features associated with this condition are presented as found in this series and compared with those observed by previous authors.

It is emphasized that the history and physical and laboratory examinations are sufficiently characteristic to allow the diagnosis to be made with a high degree of accuracy in the majority of cases. As with any condition, the entity is represented by a spectrum in every regard, and as to the cases on either end of the spectrum, one must combine a high degree of suspicion with a knowledge of the spectrum, else the true diagnosis will only be made at the autopsy table or at the time of ill-advised operative procedures.

Particular emphasis is given to the group of patients over 50 years of age who represent about 5 per cent of the patients with Ebstein's anomaly. They may be, and in fact generally are, unusual in all respects when compared to the typical case.

Comments are made on the natural history of the young patient, and it is urged that extensive diagnostic or surgical procedures be delayed until signs of deterioration appear, since tolerance of such procedures may be poor.

The etiology of the anomaly remains obscure, and a practical and satisfactory therapeutic approach remains for the future.

REFERENCES

1. Ebstein, W.: Über einen sehr seltenen Fall von Insuffizienz der Valvula Tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben, Arch. Anat. Physiol. & wissensch. Med. 238, 1866.
2. Vacca, J. B., Bussman, D. W., and Mudd, J. G.: Ebstein's anomaly: Complete review of 108 cases, Am. J. Cardiol. 2:210, 1958.
3. Mayer, F. E., Nadas, A. S., and Ongley, P. A.: Ebstein's anomaly: Presentation of ten cases, Circulation 16:1057, 1957.
4. Schiebler, G. L., Adams, P., Jr., Anderson, R. C., Amplatz, K., and Lester, R. G.: Clinical study of 23 cases of Ebstein's anomaly of the tricuspid valve, Circulation 19:165, 1959.
5. Gasul, B. M., Weiss, H., Fell, E. H., Dillon, R. F., Fisher, D. L., and Marienfeld, C. J.: Angiocardiography in congenital heart disease correlated with clinical and autopsy findings, Am. J. Dis. Child. 85:404, 1953.
6. Brekke, V. G.: Congenital tricuspid insufficiency, Am. Heart J. 29:647, 1945.
7. Edwards, J. E.: Differential diagnosis of mitral stenosis, Lab. Invest. 3:89, 1954.
8. Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Ebstein's disease: Report of the first case diagnosed during life, Am. J. M. Sc. 222:554, 1951.
9. Lev, M., Gibson, S., and Miller, R. A.: Ebstein's disease with Wolff-Parkinson-White syndrome: Report of a case with histopathologic

study of possible conduction path ays Am. Heart J 49 724 1955.

10. Blacket, R. B., Sinclair Smith, B. C., Palmer A. J Halliday J H and Maddox, J K. Ebstein disease A report of five cases, Australasian Ann. Med. 1:26, 1952.
11. Hengel, A. Über eine besondere Form von Entwicklungsstörung der Trikuspidalklappe, Virchow Arch. path. Anat. 211:301 1913
12. Gartler R. R., Weber J W Muller P Sahli, H. R., and Cottier H. Besonderheiten beim Ebstein-Syndrom Ztschr Kreislaufforsch. 48:30, 1959
13. Michel, D Gruner G and Herbst, M Zum elektrodardiogr phischen Bild des Ebstein-Syndroms, Ztschr Kreislaufforsch. 44:531, 1955
14. Schonenberger F Über einen Fall on hochgradiger Missbildung der Trikuspidalklappe mit Insuffizienz derselben, Inaug Diss Zurich 1903.
15. Engle, M A., P ne, T P B Brown, C., nd Taussig, H. B Ebstein anomaly of the tricuspid val e. Report of three cases and analysis of clinical syndrome. Circulation 1 1246 1950
16. Broadbent, J C., Wood, E. H., Burchell, H B, and Parker R. L. Ebstein malformation of the tricuspid valve: Report of 3 cases, P oc. Staff Meet. May Clin. 28 79 1953
17. Hueck, O Eine seltene Trikuspidalismissbild ng, Virchow Arch path. Anat. 319:_47 1950.
18. Cisneros F Soberon, J Marsico, F Vinacour R and Loado, J. A caso de enfermedad de Ebstein, Arch Inst Cardiol. México 24:403 1954
19. Schaede A. Zur Diagnostik des Ebstein-Syndromes Deutsches Arch klin Med. 198:619 1951
20. Kilby R A., Dushane, J W Wood, E. H and Burchell, H. B Ebstein malformation A clinical and labor tory study Medicine 35 161 1956
21. Brown, J W Hea h D and Whitaker W Ebstein disease, Am. J Med. 20:322, 1956.
22. Walton, K and Spencer A. G. Ebstein anomal of the tricuspid val J P th & Bact. 60:387 1948.
23. Bernard, H Pequignot, H and Pestel et N taf M Maladie d Ebstein et stenose tricuspidienne bien tolerée pendant cinqua te cinq ns chez une mere des enfants, Bull. et mém Soc méd hôp. Paris 70:858 1954.
24. Oldenburg, F A and Nichol, A. D Ebstein anomaly in the adult, Ann. Int. Med. 52 710 1960.
25. Marxsen, T Ein seltener Fall von Anomalie de Tricuspidalis Inaug Diss Kiel, 1886.
26. Malan, G Über die Entstehung eines Herzgeräusches Centralbl. f allg. P th. u. path. Anat 19:452, 1908
27. Lenegre, J Cattoir E and Gerbaux, A. Contribution à l'étude de la maladie d'Ebstein Arch Mal C eur 48:61_, 1955
28. Sinha, K P Uricchio, J F and Goldberg, H. Ebstein syndrome, Brit Heart J 22:91 1960
29. Van Buchem, E S. P Nieveen, J Van Der Stikkl, L. B and Gerritsen, J W Ebstein disease Cardiologica 37 129 1960
30. Lowe W R. Clinical and physiologic studies in Ebstein malformation. Am. Heart J 57 701, 1959
31. Mcdd, W E Matthews M B and Thursfield, W R. R. Ebstein disease, Thorax 9 14, 1954
32. Gotsche H. and Falholt, W Ebstein anomaly of the tricuspid val e A review of th literature and eport of 6 new cases, Am Heart J 4 :587 1954
33. Bauer D deF Ebstein type of tricuspid insufficiency Roentgen studies in case w th sudden death t the age of 27 Am. J Roent genol. 54 136 1945
34. Good in, J F Wynn, A. and Steiner R. E Ebstein anomaly of the tricuspid valve Am Heart J 35 144 1953.
35. Blount, S. G., McCord. M C and Gelb, I S Ebstein anomaly Circulation 15:_10 1957
36. Williams R. S., and Carmichael, J A. Q Ebstein disease A case report, Roy l Army Med. Corps J 104:233, 1958.
37. Kezdi, P and Wennemark, J Ebstein malformation Clinical findings and hemodynamic alterations Am J Cardiol. 2:200 1958.
38. Henderson, C B Jackson F and Swan W G A. Ebstein anomaly diagnosed during life, Brit. Heart J 15:360 1953
39. Yater W M od Shapiro, M D Congenital displacement of the tricuspid alve (Ebstein disease) Review and eport of case ith lectrocardiographic abnormalities and detailed histologic stud of the conduction system Ann Int. Med 11 1043 1937
40. Baker C Brinton, W D and Channell G D Ebstein disease Guy Hosp Rep 99:_47 1950.
41. Coets, C. E., and Warren, J E The Ebstein anomaly Acta Cardiol. 11:339 1956
42. Reynolds, G Ebstein disease A case diag nosed clinicall Guy Hosp Rep 99:276, 1950
43. Emmrich J Cook Sup So Steem, H and Reindell, H Phonocardiographische bef ndo beim Ebstein syndrome, Cardiologica 37 10 1960.
44. Zak F Z., Sum P and Larosa, C A Case report Ebstein disease New York State J Med. 55:_519 1955
45. Sodi-Pallares D and Marsic F The importance of electrocardiographic pa ern in congenital heart disease Am He rt J 49:20 1955
46. Gr ux, P and Merlin, J F A propos d un cas de maladie d'Ebstein. Arch Mal Coeur 44:263 1951
47. Adams J C I and Hudson, R A case of Ebstein anomaly surviving t the age 79 Brit. Heart J 18 129 1956
48. Harris R. H D Ebstein anomal Discovered in 75-year-old subject the dissecting labora ory Canad M A J 83:653 1960
49. Pechstein, J Beitrag zur Ebsteinschen Anomalie der valvula tricuspidalis (On Ebstein

anom ly of tricuspid valve) Arch Kr isl f forsch. 26:282 1957
50. Van Lingen, B and Bauersfeld S R The electrocardiogram in Ebstein anomaly of the tricuspid al Am. H art J 50 13 1955
51 Sodi Pallares D New bases of elect d ag phy St Louis 1956 The C V Mosby Com pan p 270
52 Hernande F A Rochk nd R nd C oper H R The intrac ltary elect ar rd ae the diagnosis of Ebstein om n l Am J Cardiol 1 181 1958
53 Gotshalk, H C C H d M H C Elect ocardiogr phic h nges d be lncreas with malformed t pid l J A M A 155 1411 1954
54 Ampl tz, K Lest R C Schiebler C l Adams F J d Ander K C The roentgenologic f tures of Ebstei anom l of the tricuspid A J Roentge ol 81 788 1959
55 Kilstm A D l l M nd Bragulio, A l Ebstein m l of the t uspid h Angiocardiogr ph d s is Am H art J 50:634 1955
56 Soloff L A St ull H M nd Z tuch J Ebstei disease Di ptions of the heart of the first ase diagnosed during lif Am J M Sc 233:23 195
57 Blou t S G Ebstei nomal Zimmer ma H A ed t r l t ascul theteriz tion, Springfield, Ill 1959 Charles C Th mas p 319
58 Kernl A J Ebst nom l Report of se diagnosed dur ng lf B t Hea t J 1 109 1955
59 Van B J B nd Yu, I N A fue of n elect ode theter m d gnosis of Ebstei disease Cir ulation 1 :513 1958
60 Kjellberg, S R M nheimer E Rudhe L nd Jonsson B Diagnosis of ongen tal heart disease Chicago 1958 Year Book P blishers Inc p 518
61 Sancett S M nd Zimmerm n, H A C ngen tal he rt dise se with septal defect l which pa adoxic l bra bscess uses death, Circulation 1:593 1950.
62 Barger J D Henderson, C I nd Edwards, J E Abscess of the brain l ad lt with Ebstein malformation of the tricuspid l Am. J Clin P th 21:376 1951
63 Keith, T A and Lyon, S A Hemophilus ph oph lus ndocard t s, Am J Med 34:535 1963.
64 Ed nds J E l thologic f t res of Ebstein malformation of the t icuspid v lve Proc Staff Meet M y Cl 28:87 1953
65 V n Mierop, L H S Alley R D Kausel, H W and Stranahan, A Ebstei malformation of the left trioventricula v l in corrected t nsposit on, ith ulpulm nary tenosis nd ventricular septal defect Am J Cardiol. 8:270, 1961
66. Lev M nd Rowlett R F: The pathologic anatomy of mixed levocardia A review of thirteen cases of at lal w entricular in ersion with or without orrected tr nspo ition, Am. J Cardiol 8:216, 1961
67 Hunter S W and Lillehei, C W Ebstein m lformation of the tricuspid valve. Study of case together ith uggestion of a new form of urgical therapy Dis. Chest 33:297 1958
68 Gasul, B. M Weinberg M J Luan L. L. Fell, E H Bicoff J and Steiger Z. Superior vena cava—right main pulmonary artery anastomosis, J.A.M.A. 171 1797 1959
69 Gasul, B M Weinberg, M J Leodrum, B L., and Fell, E H Indications for and evaluation of surgical therapy in congenital heart disease Prog Cardiovas. Dis 2:263, 1960
70 McCredie, R. M Oakley C., Mahoney E. B and A F N Ebstein disease Diagnosis by lectrode catheter and treatment by partial bypass of the right ide of the heart, New England J Med. 267 174 1962.
71 Scott, L. P III Dempsey J J Timmis H H nd McClenathan, J E. A surgical approach to Ebstein disease Circulation 27:347 1963
72. Kettle A. M Holmsworth J A., Kaplan, S and Ogden A. E. Experience with anastomosis of superior vena cava t pulmonary artery (Glenn procedure) Circulation 27 733, 1963
73 Wei berg M J Bicoff J P Agustsson, M H Steiger Z Gasul, B M Fell, E. H and Luan L. L. Surgical palliation in patient w th Ebstein anomaly and congenital hypo pla ia of the right ve tricle J Thoracic & Cardiovas. Surg 40:310 1960.
74 Barnard C N and Schrire V Surgical correction of Ebstein malformation with prosthetic t icuspid valve Surgery 54:302, 1963.
75 Caddell J C and Browne, M J Right ventricular hypertension nd pulmonary stenosis in Ebstein nomaly of the heart, Am. J Cardiol. 11 100 1963
76. Perloff J K. Cardiac catheterization clinical discipline illustrated by a study of Ebstein's anomaly of the tricuspid val Med. Ann D C 31:342 1962.
77 F y J E Fransma S. L., and Parker J O: Tw ncy notic cases of Ebstein disease J Canad Ass. Radiol. 18:48, 1964
78 Jacobs W J Jr and M I tosh, H. D and Moles S S. Ebstein m lform tion De orda t int ervit ry electrocardiographic and pressure latlonship, Am. J Cardiol. 11:770, 1964
79 A Buchem F.S.P Nieveen, J Van der Slikke L B. nd Gerritsen, J W Ebstein disease Three cases of acyanotic form, Cardiologia 37 129 1960
80. Case records of the M ssachusett General H pital Case 61 1963 New England J Med 269:691 1963.
81 Hipona, F A and Arthachinta S. Ebstein anomaly of the tricuspid valve A report of 16 cases and review of the literature Prog Ca d m Dis 134 1965.
82 G ndhl, M J nd D tev h. K. The abs of elect ophy iologic hanges at the tricuspid v lve in the diagnosis of Ebstein anomaly Am. J Cardiol. 1 169 1963
83 Schiebler G. L., et al.: Congenital corrected transp ition of the gre t vessel A study of 33 cases Pediatrics 27:851 1961

84. Roberts, W. C., Ross, R. S., and Davis, F. W. J. Congenital corrected transposition of the great vessels in adulthood simulating rheumatic valvular disease. Bull. Johns Hopkins Hosp. 114 157, 1964.
85. Berry, W. B., Roberts, W. C., Morrow, A. G., and Braunwald, E. Corrected transposition of the aorta and pulmonary trunk. Clinical, hemodynamic and pathological findings, Am. J Med. 36:35, 1964.
86. Dekker, A., Mehrizi, A. and Vengsarkar, A. S. Corrected transposition of the great vessels with Ebstein malformation of the left trioventricular valve, Circulation 31 119, 1965.
87. DeLeon, A. C., Perloff, J. K., and Blanco, P. Congenital pulmonic stenosis complicating Ebstein's anomaly of the tricuspid valve, Am. J Cardiol. 14:695, 1964.
88. Ferguson, C. C., Cumming, G. R., and Whytehead, L. L. Superior vena cava to pulmonary artery anastomosis for selected congenital lesions of the heart, Canad. J Surg. 7 120, 1964.
89. Cartwright, R. S., et al. Total correction of Ebstein's anomaly by means of tricuspid replacement, J. Thoracic & Cardiovas. Surg. 4 755, 1964.
90. Watson, H. Electrode catheters and the diagnosis of Ebstein's anomaly of the tricuspid valve, Brit. Heart J 28 161, 1966.
91. Guerón, M. et al. Familial Ebstein's anomaly with emphasis on the surgical treatment, Am. J Cardiol. 18 105, 1966.
92. Makous, N. and Vander Veer, J. B. Ebstein's anomaly and life expectancy, Am. J Cardiol. 18 100, 1966.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reappraisal of digitalis. Part VII. Indications for digitalis

*Alan F. Lyon, M.D.**
*Arthur C. DeGraff, M.D.***
New York, N. Y.

The multiple clinical uses advocated for digitalis fall into two major categories: those dependent on its favorable effect on congestive heart failure and those based on its effect on cardiac rhythms. In each category there are uses that are well established and undisputed and others that are the subject of controversy.

Three decades ago digitalis was thought by many to be useful in congestive heart failure only in the presence of atrial fibrillation; now it is universally agreed that digitalis is of value in the treatment of full-blown congestive heart failure associated with regular sinus rhythm, regardless of the etiology of the heart disease. There is also general agreement that continuing maintenance therapy is of value in maintaining cardiac compensation. The value of digitalis has extensive hemodynamic documentation, particularly in initial digitalization. Patients with primary myocardial diseases, such as alcoholic cardiomyopathy, and other less well-defined clinical entities, have in the past been thought to be unresponsive to digitalis or so prone to arrhythmias as to be unsuitable subjects for the use of digitalis. There is now adequate clinical and hemodynamic evidence to establish that digitalis is very effective in these patients, in infants as well as in adults, and that on the average these patients are no more subject to the cardiac toxic effects of digitalis than are any other patients. A form of combined left and right ventricular failure which occurs usually in children with ventricular septal defect and patent ductus arteriosus responds very well to digitalis. In cor pulmonale, especially the anoxic type due to bronchitis and emphysema, there has always been considerable doubt on clinical grounds whether digitalis is effective. Rapid digitalization during cardiac catheterization, however, has shown improvement in cardiac function in these patients even with high output failure. It has been reported that digitalis is more likely to produce arrhythmias in the hypoxic patient, which indicates the importance of correcting hypoxia as early as possible in these patients. Other forms of right-sided failure, such as occur in pulmonic stenosis and atrial septal defect, are regularly improved by digitalis.

Quite different is the response of those types of congestive heart failure that can be considered to be circulatory congestion: the high cardiac output states seen in severe anemia, beriberi, arteriovenous fistula, and the expanded blood volume type of heart failure of acute renal shutdown

Received for publication Dec. 1, 1964.

*Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N. Y.
**Professor of Therapeutics, New York University College of Medicine, and Consultant in Cardiology, Veterans Administration Hospital, Bronx, N. Y.

and acute glomerulonephritis. These states, even when they are associated with elevated intracardiac volumes and pressures are not at all benefited by digitalis. Similarly obstructive states associated with circulatory congestion but not with ventricular decompensation are not helped by digitalis. Constrictive pericarditis is not usually affected favorably by digitalis, unless atrial fibrillation or flutter is present as well Pure mitral stenosis without right ventricular failure also falls into this category In this condition the only way that digitalis could conceivably help the patient in normal sinus rhythm would be by markedly increasing the force of left atrial contraction. That atrial contraction is important in maintaining flow in these patients is demonstrated clinically by the marked deterioration that occurs so frequently when these patients develop atrial fibrillation. Moreover it has been shown that digitalis can increase the force of atrial contraction in vitro and that it can increase that maximal dp/dt of the a wave in vivo (a crude index of the speed of contraction and thus of contractility) Nonetheless, hemodynamic studies of the effect of digitalis on cardiac function in patients with pure mitral stenosis, sinus rhythm and no right ventricular failure have shown no improvement from digitalis. This is consistent with clinical observations in these patients. When mitral stenosis is complicated by right ventricular failure digitalis can certainly increase the cardiac index by improving right ventricular function. It has been observed that digitalization in this group of patients may lead to increased pulmonary arterial pressure this is not unexpected since flow is increased without relieving the obstruction at the mitral valve Although this could conceivably increase the likelihood of pulmonary edema, we are of the opinion that this is not a serious problem and that digitalis should be used Actually the situation is a rare one since patients with mitral stenosis and right ventricular failure nearly always have atrial fibrillation and must be digitalized on that basis. A unique form of obstruction is the muscular obstruction seen in idiopathic hypertrophic subaortic stenosis. It has been reported that the increased contractility produced by digitalis can lead to increased obstruction and worsening of the patient's condition. Therefore digitalis is considered to be contraindicated in this condition

Digitalis in subclinical failure When diseases of the heart in which digitalis is indicated are associated with gross congestive heart failure with distended neck veins, hepatomegaly and edema, there is no question of the need for digitalis However on clinical grounds, there is no doubt that patients who have not progressed to this advanced state of heart failure are often helped by digitalis. Thus patients whose only symptoms are those of exertional dyspnea or even of persistent fatigue are helped by digitalis when their symptoms are due to ventricular dysfunction. Since these symptoms can be produced by many conditions other than ventricular dysfunction it is important to try to define what constitutes such dysfunction and which patients, therefore should be digitalized The advent of precise and objective hemodynamic studies has obscured rather than clarified the distinction between congestive heart failure and normal cardiac function by demonstrating that the differentiation between normal function and heart failure is complicated It has been demonstrated that, in the case of the high-output states elevated intracardiac pressures can occur without real ventricular dysfunction and that digitalis does not help these patients Conversely it has been shown that real congestive heart failure can occur with dilatation of the ventricles but no increase in ventricular diastolic pressures. When this occurs on the right side congestive heart failure is observed and the need for digitalis is accepted When this occurs only on the left side and is manifested only by exertional dyspnea, cardiomegaly and gallop rhythm digitalis is definitely of benefit The situation is more difficult to evaluate when the patient denies symptoms. In heart diseases not associated with elevated systolic intraventricular pressures such as arteriosclerotic and primary myocardial disease the presence of a gallop rhythm reflects ventricular overfilling and increased cardiac muscle stretch Since this probably reflects a considerable degree of ventricular dysfunction it would seem

to be logical to use digitalis in such patients.

The indication for digitalis in patients whose only manifestation of cardiac dysfunction is a presystolic gallop in conditions with high intraventricular systolic pressures is still less clear. Here the presystolic gallop seems to reflect very forceful atrial contraction. This is an efficient compensatory mechanism that need not be associated with gross dilatation of the heart. When the presystolic gallop occurs in the presence of systemic or pulmonary hypertension, it seems to be more appropriate to lower the pressure by means of antihypertensive drugs in the one case and by treatment of pulmonary disease in the other than to use digitalis. In the case of aortic stenosis surgery is the only means available for lessening the ventricular overload that the presystolic gallop reflects, so that it might seem to be logical to protect the patient against stresses by the use of digitalis. Experimental support for this view can be found in a study that showed that digitalized rats with artificial aortic stenosis developed less ventricular hypertrophy than did the nondigitalized controls. Nonetheless clinical data to confirm that such patients are helped by digitalis are difficult to obtain and it is not our practice to use digitalis in such patients when they are asymptomatic.

No good experimental data exist to support the use of digitalis preoperatively. There is, however, good evidence that various anesthetic agents depress cardiac contractility and that digitalis can largely counteract this depression. It has been suggested, therefore, that patients whose underlying heart disease makes them prone to develop heart failure at the time of surgery should be prophylactically digitalized. This has been suggested especially for patients about to undergo heart surgery, in whom both ventriculotomy and circulatory congestion may precipitate heart failure. Nonetheless, the issue is unclear because this same surgical stress may be associated with electrolyte imbalance that can lead to arrhythmias. This hazard must be balanced against the potential benefit of improved contractility. Since no large-scale controlled clinical study has been made in order to find a clinical answer to this unresolved question, no final answer can be given. It is our practice to withhold prophylactic digitalis in such cases and to use it postoperatively when necessary.

Digitalis in acute myocardial infarction. Acute myocardial infarction so increases the likelihood of digitalis-induced arrhythmias that it has long been a relative contraindication to the use of the drug. When acute pulmonary edema that is refractory to other therapy complicates acute myocardial infarction, however, the benefit of cautiously administered digitalis is generally accepted. Its use in the cardiogenic shock of acute myocardial infarction is more controversial. Since a reduction in cardiac contractility and output is the major cause of such shock, the hemodynamic effects of digitalis would seem to be appropriate. There are, moreover, a number of case reports of patients with both shock and pulmonary edema which document a rise in blood pressure as well as relief of dyspnea when digitalis was administered. What is lacking is a controlled study of digitalis in cardiogenic shock without gross pulmonary edema which can support the contention that its hemodynamic advantages outweigh the hazard of arrhythmia. Until such a study is available, the use of digitalis in cardiogenic shock must be considered to be experimental.

Digitalis in arrhythmias. The use of digitalis to control the ventricular rate in patients with established atrial fibrillation needs no justification or discussion. It has been partially supplanted by synchronized precordial shock in the treatment of acute atrial fibrillation, but is still most valuable in this condition when, for one reason or another, shock cannot be used. Since few patients are allowed to persist in chronic atrial flutter and since precordial shock is so effective in atrial flutter, digitalis has been largely replaced in the treatment of this arrhythmia. One group has observed that a small amount of digitalis reduces the immediate recurrence rate of atrial flutter and is therefore valuable in this arrhythmia. This has not been our experience.

Digitalis is now rather low in priority for the treatment of other arrhythmias, being reserved for those atrial tachycardias refractory to vagal maneuvers, vasopres-

sors and precordial shock and having no place in the treatment of ventricular tachycardia and atrioventricular block. The notion that digitalis can be valuable in patients with transient complete atrioventricular block by stabilizing the block is not supported by clinical experience. In general this fixing of th block does not occur and the patient s condition may be worsened by increased sensitivity of the carotid sinus reflex.

Digitalis is generally dangerous in complete atrioventricular block since it can lead both to slowing of the rate and to ventricular fibrillation Indeed in patients with Stokes-Adams seizures on the basis of either transient fibrillation or transient standstill it is contraindicated at least until an internal pacemaker is functioning

In patients with congestive heart failure and stable complete heart block, digitalis, used cautiously can improve the cardiac output and the patient s condition and is therefore not absolutely contraindicated

REFERENCES

1 Schwartz, L. S and Schwartz, S. P The effects of digitalis bodies on patients with heart block and congestive heart failure, Prog Cardiovas. Dis, 6:366, 1964.

2. Goldberg, A. H., Maling, H M and Gaffney T E. The value of prophylactic digitalization in halothane anesthesia, Anesthesiology 23:207 1962.

3 Gorlin, R and Robin, E. D Cardiac glycosides in treatment of cardiogenic shock, Brit. M J 1:937 1955.

4 Elkins, L. W Circulatory congestion and heart failure, Circulation 22:864 1960.

Annotations

Rheologic changes in myocardial infarction

The blood is an organ which possesses the unique quality of constant motion, the direct result of the work performed by the heart. Although the precise application of Poiseuille's law to circulatory problems is impossible, the broad relationships are nonetheless pertinent to the extent that the work required of the heart to maintain this flow of blood is directly proportional to the viscosity of the blood. Blood also is a delicately balanced suspension of free cellular elements in a fluid medium which possesses the properties of a pseudoplastic such that *the slower the rate of flow the greater is its viscosity.* The viscosity of blood is determined by (1) the viscosity of plasma, (2) the internal sol-gel viscosity of suspended cells, and (3) the number, surface area, and surface charge of the red cells. The greatest contribution to the viscosity of blood, especially at the slower flow rates, is made by the last factor.

Because of the high incidence of visible intravascular sludging in the conjunctival capillary bed in acute myocardial infarction, serial determinations of plasma proteins were made. These measurements showed a gradual increase in alpha 1 and alpha 2 globulins and fibrinogen, a decrease in albumin, and no change in the beta or gamma globulins. The changes were progressive during the first 4 or 5 days of the illness and corresponded in time with the elevation of the erythrocyte sedimentation rate. Similar variations in plasma proteins have been reported in other forms of tissue injury, all associated with deterioration in the suspension stability of blood.

Loss of suspension stability, called cellular aggregation or sludging, lowers the viscosity of the blood by reducing the cell surface area but also impairs the efficiency of transport of the total red cell mass, and the facility with which red cells negotiate the microcirculation.

In acute myocardial infarction the viscosity of the blood is a crucial consideration to the severely injured pump, which may be greatly magnified by the frequently observed reduction in cardiac output. Cellular aggregation lowers the viscosity of the blood but introduces new restrictions on perfusion effectiveness generally and notably in the area of potential coronary collaterals. Since the presence of these changes is reflected in determinations of viscosity of blood and of hematocrit, serial daily measurements were made in cases of acute myocardial infarction treated by accepted methods.

Observations. Three basic patterns of change were noted. In mild cases of myocardial infarction there was a prominent increase in the viscosity of blood that reached its peak by the second or third day with a gradual return to normal levels within about 1 week, with no reduction in hematocrit. This change represented an acute strain on the injured heart. If the cardiac reserve could not accommodate this increased strain, the mean flow rate must be presumed to fall with further increase in the effective viscosity of the blood.

In the average case of myocardial *infarction* there was a sharp fall in viscosity on the second day of illness, with either no change or an increase in hematocrit. The viscosity of the blood returned to higher levels by the third day and then gradually decreased to more normal levels by the end of 1 week. This pattern of change was due to temporary cellular aggregation with reduction of cell surface area. The aggregation reduced the work of the heart and probably permitted survival, but also reduced the effectiveness of the red cells in transporting oxygen and CO_2.

In more severe cases there was a progressive fall in viscosity as a result of cellular aggregation followed shortly by a fall in hematocrit due to sequestration of red cell clumps in the microcirculation. *These changes significantly reduced the work of the* heart but unfortunately also resulted in effective loss of red cells, reduction in metabolically active surface area, and blockage of areas of the microcirculation. Seventy per cent of the patients who survived for more than 1 week showed the second pattern.

Therapeutic objectives. The object of therapy was to prevent the acute increase in the viscosity of the blood in order to reduce the strain on the injured heart and make unnecessary natural compensation by cellular aggregation, with its highly undesirable secondary effects. One group of patients was hydrated with 5 per cent glucose in distilled water, approximately 1,500 c.c. daily for the first 3 days of the illness. This group showed the same three patterns of change with a slightly increased incidence of the less severe patterns. A second group of patients was given 10 per cent low molecular weight dextran in 5 per cent glucose for 3 days, approximately 1,500 c.c. daily. All showed a uniform reduction in both viscosity and hematocrit during the infusion with none of the changes indicating cell aggregation or sequestration.

The conclusion was that gross changes in the viscosity of the blood and in the cellular suspension stability of blood occur within the first few days in

Supported in part by Grant HE 08231-01 S1 from the National Institutes of Health, United States Public Health Service and by a grant from the Lola Wright Foundation, Austin, Texas.

cases of acute myocardial infarction, which may materially affect heart strain and perfusion of the microcirculation. Improved hydration alone had very little effect on these patterns. Low molecular weight dextran greatly influenced both the viscosity of the blood and the cellular aggregation phenomenon in a manner which might logically be beneficial.

Per H. Langsjoen, M.D.
Thomas W. Inmon, M.D.
Department of Cardiovascular Diseases
Scott & White Clinic
Temple, Texas

REFERENCES

1. Dintenfass, L.: Rheologic approach to thrombosis and atherosclerosis, Angiology 15:333, 1964.
2. Bloch, E. H.: In vivo microscopic observations of circulating blood in acute myocardial infarction, Am. J. M. Sc. 229:280, 1955.
3. Gelin, L. E.: Studies with anemia of injury, Acta Chir. Scandinav. Suppl. 210, 1956.

The pattern of congenital heart disease in Yoruba children of Western Nigeria

A brief clinical survey of congenital heart disease in Yoruba children of Western Nigeria was conducted at the University College Hospital from November 1963 to June 1965. Clinical diagnoses were made with the aid of electrocardiograms recorded on a Transistia III Cambridge machine, chest roentgenograms for cardiac size and configuration, and a limited number of angiocardiograms. Some of the diagnoses were confirmed at the time of operation or autopsy examination.

Sixty-seven children ranging in age from newborn to 12 years of age were evaluated; most of them were under 2 years of age. The diagnoses of this small series are listed in Table I. It can be seen that the two most common lesions were ventricular septal defect and patent ductus arteriosus, and that most of the expected lesions were represented. Ebstein's anomaly might have been misdiagnosed as right ventricular endomyocardial fibrosis, which it closely resembles. Cases of atrial septal defect could have been overlooked in the busy pediatric clinics from which most of the referrals were made, since this lesion is relatively asymptomatic during childhood and is accompanied by no prominent murmur. Infants with cyanotic heart lesions, such as transposition of the great vessels or tetralogy of Fallot, might have been considered to be too ill for a long bus journey to the hospital.

The true incidence and distribution of congenital heart disease in the tropics and subtropics are not known. In many regions there are no accurate figures on birth and death rates or on the causes of death. Sick children are often treated only by medicine men. It is understood that many die at home.

This small sample of children with congenital heart lesions cannot be regarded as being a truly accurate cross section of the problem, but it helps to confirm the conclusions of observers in South Africa, Jamaica, Singapore, and Uganda that the distribution of congenital heart disease in the tropics and subtropics is probably not different from that in the temperate zone.

Table I. Congenital heart lesions in 67 Nigerian children

Ventricular septal defect	26
Patent ductus arteriosus	14
Atrioventricularis communis	6
Pulmonary stenosis	4
Tricuspid stenosis or atresia	3
Dextrocardia	3
Tetralogy of Fallot	2
Aortic stenosis	2
Aortic atresia	1
Transposition of the great vessels	1
Total anomalous pulmonary venous return	1
Diagnosis unknown	4

*Joan I. Caddell, M.D.**
Department of Physiology
George Washington University
1339 H St., N.W.
Washington, D.C.
Patricia Morton, M.D.
Consultant Physician
Department of Cardiology
Belfast City Hospital
Belfast, Northern Ireland

This work was supported by the Rockefeller Foundation through Special Grant GA MNS 6401 (3).

*Former Rockefeller Foundation Fellow.

REFERENCES

1. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Company, p. 3.
2. Abrahams, D. G.: Endomyocardial fibrosis of the right ventricle, Quart. J. Med. 31:1, 1962.
3. Schrire, V.: The racial incidence of the less common forms of heart disease at Groote Schuur Hospital, Cape Town, 1952-1961, South African M. J. 38:598, 1964.
4. Walter, D. C.: Congenital heart disease in Jamaica, West Indian M. J. 9:194, 1960.
5. Muir, C. S.: Incidence of congenital heart disease [illegible] Singapore, Brit. Heart J. 22:243, 1960.
6. Caddell, J. L., and Connor, D. H.: Congenital heart disease in Ugandan children, Brit. Heart J. 28:766, 1966.

Plantain diets, serotonin, and endomyocardial fibrosis

The fibrotic lesions of carcinoid heart disease are associated with the high level of serotonin in the blood and the excretion of large amounts of 5-hydroxyindoleacetic acid (5-H.I.A.A.) in the urine. The African plantain contains large quantities of serotonin and in a speculative mood Arnott reflected on the possibility of the plantain diet being a factor in the production of endomyocardial fibrosis (EMF). He considered it unlikely but thought that the possibility of harmful substances in the food being implicated in EMF could not lightly be dismissed. From this "final note" has followed a large number of investigations into the possibility that the plantain diet is a significant factor in the pathogenesis of EMF. This annotation is a brief review of the studies in this field carried out up to the present time.

In both East and West Africa a high intake of serotonin in plantain has been shown to be associated with high excretion rates of 5-H.I.A.A. in the urine. The concept in the background of these studies is that if 5-H.I.A.A. excretion can be taken as a measure of the circulating serotonin the plantain-eating Africans are subjected to stress similar to the argentaffinoma patients. There is, however, no evidence as yet that the high level of urinary 5-H.I.A.A. excretion in East and West Africans are associated with high levels of circulating serotonin. Crawford has speculated on the various complex [illegible] which the plantain might possibly be of pathologic significance and concluded that "the evidence suggests that serotonin by itself is not of importance."

Melmon and Sjoerdsma found that the oral administration for 18 days of up to 160 mg. of serotonin, either as the drug or in bananas, caused the platelet-serotonin content to rise 2.5 to 6.0 fold. When the dosage was stopped the level dropped gradually to half its value in 3 days. They consider that their findings support the further study of the role of serotonin in the development of EMF. Their choice of dosage level was apparently based on the data of Crawford from which they calculated that the daily intake of 5-hydroxytryptamine (5-H.T.) by African subjects might be as high as 200 mg. However, Foy and Parratt[4] found that the plantain pulp contained about 50 μg per gram of 5-H.T. and estimated that the total daily ingestion of 5-H.T. from cooked plantain meals in Western Nigeria was between 20 and 40 mg. Crawford quotes a figure of 400 to 800 Gm. of pulp taken once or twice daily and this could give a maximum intake of 80 mg. of 5-H.T. per day. However, recorded information indicates that in young African subjects the average helping of cooked plantain is about 250 Gm. taken twice daily, which would give an intake of 5-H.T. of only 25 mg. per day. The very high level used in the study of Melmon and Sjoerdsma is probably far beyond the levels actually ingested in East and West Africa and makes the relevance of this particular experiment to the EMF situation somewhat uncertain.

Ojo and Parratt have recently studied 20 Nigerian patients with confirmed EMF and compared their ability to metabolize the 5-H.T. present in plantain meal with that of normal Nigerians, Europeans, and a miscellaneous group of patients with rheumatic heart disease and heart-muscle disease (cardiomegaly of unknown origin). The patients with EMF excreted significantly less 5-H.I.A.A. in a 20-hour period than did the control Nigerian or European subjects and the rate of 5-H.I.A.A. excretion was considerably slower in the patients with EMF. However, the patients with rheumatic heart disease and heart muscle disease excreted even less 5-H.I.A.A. in the 20-hour period than did the EMF group and their rate of 5-H.I.A.A. excretion was equally slow. The same results were thus obtained in the EMF and the miscellaneous cardiac groups but the authors conclude that their findings in the subjects with EMF are due to impaired metabolism of 5-H.T. and that, in the other

forms of heart disease studied, the low urinary values of 5-H.I.A.A. were contributed to by delayed renal excretion. T the impartial observer the results suggest ery strongly that the impaired metabolism of 5-H.T in both groups was the result of hepatic congestion, since the liver has by far the highest concentration of monoamine oxidase of any human tissue.

I support of their hypothesis that the impaired metabolism of 5-H.T is the cause rather than the result of the cardiac lesions, Oj and Parratt refer to the work of Donaldson nd his colleagues[10] and state that "It has by no means been conclusively demonstrated that even gross liver damage results in abnormal 5-H.I.A.A. excretion normal urinary values hav been reported in severe li er cirrhosis. It is true that Donaldson nd his colleagues found that the *endogenous* urinary excretion of 5-H.I.A.A. in subjects with hepatic cirrhosis did not differ from that of healthy subjects. However when 5-hydroxytryptophan (5-H.T.P.), the precursor of serotonin was administered intravenously to healthy subjects and to cirrhotic patients there as a striking difference in the excretion of 5-H.I.A.A. suggesting that *exogenous* serotonin metabolism is not normal in subjects with hepatic dysfunction.

I serotonin capable of producing cardiac lesions in laboratory mals?

Bulle (1957) injected serotonin into the left ventricular myocardium of the isolated and perfused rabbit heart and induced "infarcts hich were f lly developed within 20 minutes and disappeared after 45 mi utes. This hardly resembles EMF and the use of this reference to support the hypothesis that plantain diet may be responsible for the lesions of EMF seems t be somewhat inappropriate.

By combining raised serotonin lev l, periodic deficiency of tryptophan, and altered liver function, Spatz[11] produced cellular fibrous tissue proliferation beneath the lining of the alves and chambers of the heart, leading to the formation of nodular and diffuse fibrous plaques. Neither hyperserotonemia nor relatively tryptophan-deficient states nor liver injury—each taken by itself—produced the intimal and endocardial lesions; the combined effects of all were necessary. These lesions resembled those found carcinoid heart disease but in certain respects ere not identical ith them. Severe liver damage or cirrhosis of the liver are not features of subjects with EMF and the relevance of this study to the EMF story is also uncertain.

McKinney and Cra ford[12] have reported briefly on an experiment in which young adult guinea pigs ere fed on plantain diet with itamin and mineral supplements for 6 day eek and with sow-weaner cubes and mixed egetables on the seventh day each eek. Endocardial lesions developed in 5 of 10 guinea pigs between 174 and 189 days, and one of these had significant myocardial fibrosis as well. These hanges did not dev lop in any of the 17 control guinea pigs. This preliminary communication gives no information in regard to the detailed procedures involved in the care and feeding of these animals nor does it indicate hich animals in the study died or were killed. There is no comment on hether macroscopic changes were present in y of the hearts or on the actual causes of death. One would also like to know for how long the animals which died were ill and what other evidence of nutritional changes were present. Because of these deficiencies, full assessment of this work must await the detailed publication of this material. The cardiac changes reported are far from specific and fibrous thickening of the endocardium has been observed in a ery ide range of cardiac disorders.

Conclusion. Although it is true that endemic endomyocardial fibrosis (EMF) and the plantain diet share a common geographic distribution, this association by itself is not sufficient to incriminate 5-hydroxytryptamine (5-H.T.) in the pathogenesis of EMF. There is at present no conv ncing evidence that the serotonin content of the plantain is a factor in the etiology of this condition.

The tudy of Ojo and Parratt[8] clearly indicates the need for adequate studies on serum levels of 5-H.T in subjects with EMF and other cardiac disorders on exposure to large amounts of exogenous serotonin and its precursors, and strongly suggests that, when these studies are carried out, subjects with EMF will behave in the same w y as subjects with other forms of heart disease and congestive cardiac failure.

A. G. Shaper, M.B., M.R.C.P.
Department of Medicine
Makerere U iversity College Medical School
P. O. Box 2072
Kampala, Uganda

REFERENCES

1. Goble, A. J., Hay, D. R., nd Sandler, M.: 5-Hydroxytryptamine metabolism in acquired heart-disease associated with argentaffin carcinoma, Lancet 2:1016, 1955.
2. Foy, J. M., and Parratt, J. R.: A note on the presence of noradrenaline and 5-h droxytryptamine in plantain, J. Pharm. Pharmacol. 12:360, 1960.
3. Arnott, W. M.: A problem in tropical cardiology, Brit. M. J. 2:1273, 1959.
4. Crawford, M. A.: Excretion of 5-hydroxy indolylacetic acid in East Africans, Lancet 1:352, 1962.
5. Foy, J. M., and Parratt, J. R.: Urinary excretion of 5-hydroxyindoleacetic acid in West Africans, Lancet 1:942, 196.
6. Crawford, M. A.: Endomyocardial fibrosis and carcinoidosis. A common denominator? Am. Heart J. 66:273, 1963.
7. Melmon, K., and Sjoerdsma, A.: Serotonin in platelets. Its uptake and disappearance after administr tion of the amine by mouth, Lancet 2:316, 1963.
8. Ojo, G. O., nd Parratt, J. R.: Urinary excretion of 5-hydroxyindoleacetic acid in Nigerians with endomyocardial fibrosis, Lancet 1:854, 1966.
9. Davison, A. N.: Physiological ole of monoamine oxidase, Physiol. Rev. 38:729, 1958.
10. Donaldson, R. M., Arabehety, J., and Gray, S. J.: I vivo studies of 5-hydroxyindole metabolism in patients with hepatic cirrhosis and in rats, J. Clin. Invest. 38:933, 1959.
11. Spatz, M.: Pathogenetic studies of experi-

ment ll induced heart lesions and their relation t the carcinoid yndrome, Lab. I vest 13:288 1964
12. M Kinne B nd Crawford, M A Evol t on of endomyocardial fibrosis, Lancet 1:657 1966.
13. Sch rtz, R. and Dean R F A. An invest gation of the daily intakes of food of individual boys t boarding school in Uganda, Brit. J Nutr 9:230 1965
14. Burgess, A. P Morton, C. and Burgess, H. J. L.: The diet of some Uganda school girls, East African M J 39:464, 1962.

The effect of unilateral nephrectomy on renal function in man

It has long been know that ilateral nephrectomy I man is followed by a increase in the volume and mass of the remaining kidney nd is compatible w th normal lifespan in the absence of residual disease of the urinary tract and remaining kidney The f nctional response t uninephrectomy has received little study ma

Friedman and associates[1] studied 5 hypertensi patients who nderwent nephrectomy for lateral renal disease Glomerular filtration rate (GFR) and effectiv renal blood flow (ERBF) 13 to 19 day and 56 t 135 day postoperatively were variably less han or more tha preoperativ alues i the same patients I these cases, hypertensi altera tion the residual kidney or compensatory hyper troph of the healthy kidney before operation, may ha influenced the response t nephrectomy I study of 14 patie ts 8 day to 23 years after nephrectom for ilateral renal disease nd 5 dditional patients th single f nctioning kidney Hogeman[2] found GFR of 63 per cent d ERBF of 63 per cent f expected normal I another study of 56 patients with prior uninephrectomy endogenous creatinine learance was greater tha 100 ml. per minut in 35 nd greater tha 150 ml. per minute in 14 It is pparent therefore that increase I f nction of he remaining kidney frequently follows unilateral nephrectomy

\ inverse relationship bet een function and ge t the time of nephrectomy or t the t me of study after nephrectom has been demonstrated, imply ing a diminished functional response t ninephrec tomy in older patient I these studies however separation of this effect from other factors causi g reduced renal f nction, i.e residual renal disease or severe h pertension not possible. \ cor rection was made for the now well-know progressive diminution in renal clearances with increasing age over 40 y ars in normal individuals. There is no conclusiv work in ma indicating impaired response of the remaining kidney t unilateral neph rectomy with adv ncing age Serial tudy of maximum tubular excretion of para-aminohippurat after uninephrectomy in 74-year-old ma demon trated marked increase in this f nction which compared fa orably with th findings in 2 younger patients in terms of per cent increase.

There has been little previous study concerning the rate of increase i f nction of the remaining kidney after ilateral nephrectomy in man The mechanism of this increase and its relationship to hyperplasia or hypertrophy of the human kidney is obscure Diminished renal functional reserve, vascular alterations, and h moral growth factors [4] ha been suggested by animal studies.

The consequences of uninephrectomy have been extensively investigated in animals. I the rat, hypertrophy of convoluted tubule cells is routinely observed within 24 hours of ninephrectomy I another study of the rat, renal mass reached 65 per cent of prenephrectomy values 5 day after opera tion nd 90 per cent t 40 days after nephrectomy [10] Hyperplasia, demonstrated by proximal tubular mitotic rate, was increased elevenfold over control values 40 hours after nephrectomy in the rat. I the same animal, the ptake of tritiated thymidine by t bule cells increased 100 per cent t 48 hours after nephrectomy A prompt increase in renal function follows uninephrectomy I the dog urea clearances reached 65 t 70 per cent of preoperati levels w thin 3 eeks of nephrectomy and renal blood flow increased progressively to 75 to 85 per cent of preoperativ function 1 month after neph rectomy

The recent se of living h man donors for renal homotransplantation has afforded a unique oppor tunity t study the effect of nilateral nephrectomy on the remaining kidney Renal function wa evaluated before nd fter uninephrectomy in 29 healthy ad lt subjects with normal urinalysis repe tedly negativ rine cultures and a normal intra enous pyelogram and renal arteriogram.[16] The erage age of the patients tudied was 36.3 y rs, ith range of 21 t 52 y ars. The postoperativ tudies ere performed 1 t 18 days, with erage of 7.1 days, after nephrectomy

Blood ure itrogen (BUN) increased from a mean of 13 mg per cent before nephrectomy t 16

mg per cent afterward. Serum creatinine increased in all 29 patients, but in no instance exceeded the normal value. Mean serum creatinine increased from 0.89 mg per cent before operation to 1.19 mg per cent afterward.

Endogenous creatinine clearance, employed as an approximation of GFR, decreased in every patient but in only a single instance to less than half the initial value. Mean creatinine clearance decreased from a preoperative value of 130 ml. per minute to a value of 91 ml. per minute after nephrectomy or 70.5 per cent of the initial two-kidney function. The decrease of 29.5 per cent in this function was accurately reflected by the mean increase in serum creatinine of 33 per cent. This finding is in accord with the fact that a decrease in the clearance of an endogenous substance must be associated with a corresponding increase in serum concentration if rate of excretion and, therefore, body balance are to remain stable.

Renal plasma flow, measured as clearance of para-aminohippurate (PAH), decreased from an initial mean of 521 ml. per minute to a mean of 368 ml. per minute after nephrectomy. The postoperative mean was 70.8 per cent of the preoperative value, which agreed closely with the change in creatinine clearance. Both creatinine and PAH mean clearances after nephrectomy differed significantly ($p < 0.001$) from the theoretical value of 50 per cent of initial function which should have resulted from removal of 50 per cent of the renal mass by random uninephrectomy.

A progressive improvement in function was apparent with increasing time after nephrectomy during the short period of study. Within the age range of the patients studied, no difference in the functional response to nephrectomy was apparent.

From this study it is apparent that uninephrectomy in man is followed by an extremely rapid 40 per cent increase in the clearance of creatinine and PAH by the remaining kidney. The continued use of living human donors, when necessary for successful renal transplantation, offers further opportunity for study of the mechanism of the anatomic and functional consequences of unilateral nephrectomy in man.

David A. Ogden, M.D.
Departments of Medicine
Veterans Administration Hospital and
University of Colorado Medical Center
Denver, Colo.

Address: Dept. of Medicine, Veterans Administration Hospital, 1055 Clermont St., Denver, Colo. 80220.

REFERENCES

1. Kohler, B.: The prognosis after nephrectomy. A clinical study of early and late results, Acta Chir. Scandinav. 91 (Suppl. 94): 1944.
2. Friedman, M., Selzer, A., Kreutzmann, H., and Sampson, J. J.: The changes in the blood pressure and in the renal blood flow and glomerular filtration rate of hypertensive patients following unilateral nephrectomy, J. Clin. Invest. 21:19, 1942.
3. Hogeman, O.: Clearance tests in renal disorders and hypertension, Acta Med. Scandinav. 132 (Suppl. 216a): 1948.
4. Davies, D. F., and Shock, N. W.: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males, J. Clin. Invest. 29:496, 1950.
5. Mitchell, A. D., and Valk, W. L.: Compensatory renal hypertrophy, J. Urol. 88:11, 1962.
6. Bollman, J. L., and Mann, F. C.: Compensatory hypertrophy of the remaining kidney after nephrectomy following transplantation of its ureter into the duodenum, Arch. Path. 19:28, 1935.
7. Gross, R. J., and Rankin, M.: Physiological factors affecting compensatory renal hyperplasia in the rat, J. Exper. Zool. 145:209, 1960.
8. Lowenstein, L. M., and Stern, A.: A serum factor in renal compensatory hyperplasia, Science 142:1479, 1963.
9. Rollason, H. D.: Compensatory hypertrophy of the kidney of the young rat, with special emphasis on the role of cellular hyperplasia, Anat. Rec. 104:263, 1949.
10. Addis, R., and Lew, W.: The restoration of lost organ tissue. The rate and degree of restoration, J. Exper. Med. 71:325, 1940.
11. Williams, G. E.: Some aspects of compensatory hyperplasia of the kidney, Brit. J. Exper. Path. 42:386, 1961.
12. Kessner, D. M., and Thomas, E. D.: Renal proliferation in the unilaterally nephrectomized rat, Nature 190:175, 1961.
13. Rhoads, C. P., Alving, A. S., Hiller, A., and Van Slyke, D. D.: The functional effect of explanting one kidney and removing the other, Am. J. Physiol. 109:329, 1934.
14. Levy, S. E., and Blalock, A.: The effects of unilateral nephrectomy on renal blood flow and oxygen consumption of unanesthetized dog, Am. J. Physiol. 122:609, 1938.
15. Krohn, A. G., Ogden, D. A., and Holmes, J. H.: Renal function in 29 healthy adults before and after nephrectomy, J.A.M.A. 196:322, 1966.

Book reviews

CARDIOVASCULAR SURGERY 1965 (American Heart Association Monograph #13) Edited by F A. Simeone M D New York, 1966 American Heart Association Inc 203 pages Price $3

This monograph includes for the convenience of the reader and those who did not attend the American Heart Association meeting of 1965 in Bal Harbor Florida, 27 papers presented there Most of the material has been published elsewhere. Some surgeons may find this monograph to be useful.

CEREBROVASCULAR DISEASE Vol XLI Proceedings of Association for Research in Nervous and Mental Disease Edited by Clark H Millikan Baltimore, 1966 Williams & Wilkins Company 428 pages. Price $20 50

This is the proceedings of the meeting of the Association for Research in Nervous and Mental Disease, held New York on Dec 8 and 9 1961 Twenty-six papers are presented in this book The subjects vary considerably and include discussions of cerebrovascular pathology cerebral circulatory physiology and pharmacology diagnosis medical and surgical management of cerebrovascular disease and the usual discussions of the value of anticoagulants in treatment. Unfortunately it must be considered that this book is 5 years late in appearing in print. In spite of this, the reader will be impressed by the lack of new developments in the field. In fact the discussions at similar meetings today have changed very little This is a good book and many important problems related to cerebrovascular disease are discussed

SYMPOSIUM ON CEREBROVASCULAR DISEASE (American Heart Association Monograph #14). Edited by Robert G Siekert, M D New York, 1966 American Heart Association Inc 48 pages. Price $2.50

This monograph consists of six papers on the cerebral circulation gathered in one publication for the convenience of the reader Among the subjects discussed is a summary of the result of a Veterans Administration study of the use of estrogenic substances in the treatment of cardiovascular diseases. The drug was therapeutic failure not only for cerebral infarction but for myocardial infarction as well. In another study Eisenberg found blood viscosity to be increased in patient with recent cerebral infarction. The presentation on hyperbaric oxygen therapy extracranial vascular lesions, and cerebral hemodynamics include very little that is new

INTERASMA V—CONGRESS PROCEEDINGS Utrecht May 1966.

This paperback volume apparently puts together papers read at a conference on asthma held in Utrecht in May 1966. There is no English introduction to this book, and the purpose or emphasis of the conference is not revealed Most of the papers deal with the therapy of bronchial asthma, and include discussions on corticosteroid surgical, hormonal, and physical, climate, antihistaminic bronchodilator antibiotic and psychiatric therapy Many of the articles are in either French or German without the inclusion of an English summary The articles which are in the English language suffer generally from poor grammar sentence structure, and editing Although a few articles are of interest, such as that on the evaluation of the pulmonary function of a new bronchodilator aerosol, most of the subjects are poorly presented and the articles difficult to read It is hard to recommend the purchase of these proceedings to any group of physicians or students

VASOAKTIVE AMINE—SCHOCKBEHANDLUNG (Amines Vasoactive—Traitement du Choc. Vasoactive Amines—Treatment of Shock). Edited by J Cl. Rodler Geneve J L. Schelling Lausanne and L. K. Widmer Basel. (4e Assemblée annuelle de la Société suisse d Angéiologie en commun avec la Société suisse de Cardiologie, Lausanne, Nov 27 1965), Basel, 1966, S. Karger 136 pages. Price $10 85

This is a good series of papers on an important subject Evidence continually accumulating that vasopressor drugs can be dangerous in certain types and states of shock. Furthermore these report indicate the value of vasodilator agents in shock. The reader will find interesting evidence in regard to the action of these two groups of drugs in shock. This series of papers should be of value to physiologists and to investigators interested in shock and its management Likewise, the clinician will find this to be a rewarding book.

MECHANISMS AND THERAPY OF CARDIAC ARRHYTHMIAS (Fourteenth Hahneman Symposium). Edited by Leonard S. Dreifus, M D and William Likoff M D New York, 1966 Grune & Stratton, Inc 704 pages. Price $23

This represent the proceedings of a symposium held at the Hahnemann Medical College and Hospital during April 1965 The symposium included many presentation on a number of aspects of cardiac arrhythmias These included

(1) basis of ectopic impulse promotion, (2) identification of supraventricular arrhythmias, (3) treatment of supraventricular tachycardia, (4) genesis of ventricular tachycardia, (5) identification and treatment of ectopic ventricular mechanisms, (6) impulse formation and conduction in the atrioventricular junction, (7) identification and management of A-V block, (8) pharmacodynamics of antiarrhythmic agents, (9) cardiac monitoring and resuscitation (10) the pre-excitation syndrome and (11) metabolic derangement and cardiac arrhythmias. Several papers are presented on each of the subjects listed above, followed by panel discussions The presentations are rather brief but in general are very good The presentations and discussions reveal the many gaps in knowledge concerning the problems related to cardiac arrhythmia. This applies to therapy as well. Nevertheless, this book provides much useful information to all clinicians concerning very important and common clinical problems

PERIPHERAL ARTERIAL DISEASE. By Wiley F. Baker M.D. *Professor of Surgery University of California at Los Angeles* Vol. IV in the series, Major Problems in Clinical Surgery edited by J. Englebert Dunphy Philadelphia, 1966, W. B. Saunders Company 229 pages Price $8 50

This short book is divided into eleven chapters which include anatomy physiology pathology and pathogenesis, and diagnostic problems and six chapters on management. The major emphasis is on surgical treatment The physician who follows the literature carefully will find the book to be of little value hereas be very useful to the busy doctor The medical management is not adequately considered The surgical discussions are essentially limited to obstructive diseases of the large arteries hereas Raynaud' disease and other disease involving small arterial vessels are essentially ignored

VECTORCARDIOGRAPHY 1965 Edited by Irwin Hoffman and Robert C. Taymor Symposium held at the Long Island Jewish Hospital, New York City May 11 13, 1965 Amsterdam 1966 North Holland Publishing Company 428 pages. Price $18 20.

The symposium held in New York on May 11 13 1965 is described in this book. The investigators are primarily from the United States and represent most of the leaders in vectorcardiography today There were 59 papers and discussion panels The subjects reviewed include lead systems, display systems ventricular hypertrophy myocardial infarction, pediatric applications, and future directions of vectorcardiography The papers are well written and illustrated and have good bibliography appended The series of papers integrate very well be experimental, theoretical, technical, and clinical approaches to vectorcardiography The book also contains a tribute to Dr Herman Carel Burger of Utrecht who died shortly after the meeting. This is good book very much up to date, and highly recommended.

BALLISTOCARDIOGRAPHY AND CARDIOVASCULAR DYNAMICS. Edited by A. A. Knoop Amsterdam, Baltimore 1966, Williams & Wilkins Company 347 pages. Price $19.25

This is a good publication of the papers presented at the First World Congress on Ballistocardiography and Cardiovascular Dynamics held in Amsterdam April 12 14 1965 Fifty-seven rather brief papers were delivered at the meeting The authors, who come from many parts of the world, are active investigators in the field The subjects discussed are wide in scope, and include the methods of recording theory and dynamics of ballistocardiography physiology and pathophysiology as well as the possible clinical use of the method. Dr Starr who originated the field presented the first paper This is valuable book and should be particularly useful to all who are interested in ballistocardiography and other aspects of cardiac ballistics.

Books received

COMPARATIVE LEUKAEMIA RESEARCH. By G. Winqvist, New York, 1966 Pergamon Press, 268 pages Price $13 50

ELEKTROENCEPHALOGRAPHIE IN KLINIK UND PRAXIS By Johann Kugler Stuttgart, 1966, Georg Thieme Verlag 203 pages

SURGICAL BLEEDING By Alex W. Ulin and Seymour S. Gollub editors, New York 1966 McGraw Hill Book Co., Inc 532 pages. Price $23 50

FOOD VALUES OF PORTIONS COMMONLY USED By Bowes and Church ed 10 revised by Charles Frederick Church and Helen Nichols Church Philadelphia 1966, J. B. Lippincott Company 134 pages Price $4 50

HUMAN AS LIPID M... ANNOTATED BIBLIOGRAPHY B. M... er M. Fishman River Edge N. J. 1966 Technical Service Laboratories 95 pages

MODERN TREATMENT. Vol 3 No 3 (1 Treatment of Gastrointestinal Inf... by Marcel Patterson (2) Treatment of Superinfections b... Harold J Simon New York 1966 Hoeber Medical Division of Harper and Row 1,500 pages per year Price $16 per year

Announcements

The Department of Radiology of the University of Kentucky Medical Center is presenting a symposium on CURRENT CONCEPTS IN CHEST RADIOLOGY: PATHOPHYSIOLOGICAL CORRELATIONS, from May 1 to May 5, 1967, just before the *Kentucky Derby*. Radiologic findings will be explained in terms of basic underlying pathological mechanisms. A distinguished Visiting Faculty and staff members of the College of Medicine of the University of Kentucky will participate in the symposium. A Film Seminar will be conducted at the end of each day.

THE 7TH INTERNATIONAL CONFERENCE ON MEDICAL AND BIOLOGICAL ENGINEERING will be held in Stockholm, Sweden, August 14-19, 1967. The Conference will be held under the auspices of the International Federation for Medical and Biological Engineering and will be arranged by the Royal Swedish Academy of Engineering Sciences and the Swedish Society for Medical Physics and Medical Engineering.

The general theme of the Conference will be the new ways in which the engineering sciences have contributed to the solution of medical or biological problems. The following subjects of major practical significance will be highlighted by the arranging of special sessions: (1) engineering in accident prevention (car and flight safety); (2) tests on the new born child; (3) image processing in medical data handling; (4) medical data display systems in hospitals; and (5) materials for implants.

Simultaneously with the Conference there will be a Scientific Exhibition and Commercial Exhibition with displays of the latest equipment and instrumentation in the biomedical field.

For further information write to: Bertil Jacobson, M.D., Secretary General, 7th International Conference on Medical and Biological Engineering, Stockholm 60, Sweden.

AN INTERNATIONAL SYMPOSIUM ON THE PHARMACOLOGY OF HORMONAL POLYPEPTIDES: METABOLIC AND MOLECULAR ASPECTS will be held in Milan, Italy, on Sept. 14-16, 1967, under the co-sponsorship of the University of Milan, Institute of Pharmacology and Therapy, and the State University of New York at Buffalo, Department of Biochemical Pharmacology, School of Pharmacy, Buffalo, N.Y., and under the auspices of the International Society of Biochemical Pharmacology.

The Symposium will be divided into the following sessions: (I) Techniques in peptide synthesis. (II) Anterior pituitary and placenta. (III) Anterior pituitary and hypothalamus. (IV) Posterior pituitary hormones and factors affecting lipid mobilization. (V) Insulin and glucagon. (VI) Other hormonal peptides. Invited papers and a limited number of communications will be presented.

Deadlines. Advance registration and hotel reservations, June 30, 1967. Titles and summaries (250 words) of the free communications, May 31, 1957. Final text for invited papers, September 1967. The Proceedings will be published by an international publisher.

For information and forms contact: Secretarial Office, Profs. L. Martini and R. Paoletti, Institute of Pharmacology, University of Milan, Via Andrea del Sarto 21, Milan, Italy (telephone No. 719060).

THE 12TH BALLISTOCARDIOGRAPH RESEARCH SOCIETY MEETING will be held at Haddon Hall, Atlantic City, N.J., on April 29, 1967.

For information contact: Dr. Abraham Noordergraaf, Department of Biomedical Engineering, Moore School of Electrical Engineering, University of Pennsylvania, Philadelphia, Pa., 19104.

The National Institute of General Medical Sciences, National Institutes of Health, in cooperation with the Southwest Foundation for Research and Education, with headquarters at El Tropicano Motor Hotel, San Antonio, Tex., will hold a SYMPOSIUM ON THE USE OF SUBHUMAN PRIMATES IN DRUG EVALUATION on May 2-5, 1967.

Additional details may be obtained by writing to: Symposium Coordinator, L. Richard Smith, Jr., Southwest Foundation for Research and Education, P.O. Box 2296, San Antonio, Tex. 78206.

American Heart Journal

April 1967 Volume 73 Number 4

Editorial

Coxsackie heart disease in adults

*W. G. Smith, M.D. (Aberd.), M.R.C.P.E., M.R.A.C.P., M.R.C.P. (Lond.)**
Perth, Western Australia

Virus disease of the heart is not rare and it is now possible to confirm the diagnosis by modern virological techniques. Many viruses, such as the virus of mumps, influenza, and poliomyelitis, may involve the heart, but there is now good evidence that the six types of Coxsackie Group B viruses are the most frequent culprits. Early reports indicated that Coxsackie heart disease usually occurred in neonates and was often fatal during nursery epidemics. Some of these infants showed features similar to those in experimental animals, namely, hepatitis, nephritis, pancreatitis, and encephalitis. The first reports of Coxsackie heart disease in adults appeared in 1957 and since then increasing numbers of cases in adult patients have been reported.

The syndrome of "idiopathic acute benign pericarditis" is not uncommon and has been recognized since 1854. It is now apparent that the most frequent cause is a Coxsackie B virus. It is likely that there is always some degree of associated myocarditis and the varying increase in heart size is more often due to myocardial dilatation than to the accumulation of pericardial fluid. Youngish men appear to be especially susceptible, but, fortunately complete recovery is usually the rule, although complications may occur, such as hemopericardium, arrhythmias, pericardial constriction, and future recurrences. The term "benign" is not therefore altogether appropriate and a more accurate diagnosis is "acute Coxsackie myopericarditis."

Myocarditis may occur alone or with associated pericarditis. Complete recovery will depend on the degree of myocardial damage, any underlying coincidental heart disease such as hypertension or coronary artery disease, and also the potentially serious complications of Coxsackie B infection, such as encephalitis or hepatitis. Unexplained myocarditis, including the Fiedler type, and conditions such as idiopathic cardiomyopathy, unexplained cardiomegaly, and even subendocardial fibroelastosis, may well be a late result of previous Coxsackie heart disease.

An editorial in this JOURNAL in 1964 noted that Coxsackie B endocarditis can occur in animals and may be the cause of unexplained acute or chronic endocarditis in man. This possibility should be kept in mind before one resorts to the common empirical diagnosis of "rheumatic" endocarditis.

The diagnosis of Coxsackie heart disease

Received for publication July 16, 1966.

*Physician, Sir Charles Gairdner Hospital, Perth, Western Australia.

is made on the basis of the clinical picture which usually includes an elevated erythrocyte sedimentation rate, a *neutrophil* leukocytosis, an abnormal electrocardiogram, and possibly an abnormal chest radiograph. These features may be associated with other Coxsackie effects, such as myalgia, pleurodynia (Bornholm's disease) with or without pneumonitis, orchitis, lymphadenopathy with splenomegaly, exanthemata, and rarely encephalitis, hepatitis, pancreatitis, nephritis, and meningitis. Some of the members of the family may have recently had influenza and the Coxsackie neutralizing antibody tests should, if possible, be performed on these individuals as well as on the patient. The neutralizing antibodies should rise fourfold in paired samples of blood taken 14 to 21 days apart. It is important to note, however, that an elevated titer of, say, 1 in 40 may be seen as early as 3 days after the onset of clinical illness, so that failure to obtain a fourfold rise does not negate the diagnosis. The elevated antibody titer may persist for months or years, and this may permit a retrospective diagnosis. The height of the titer bears no relationship to the severity of the illness, and the child with mild influenza may well have a higher titer than the father with Coxsackie heart disease. Unlike Coxsackie heart disease in neonates, the initial viremia is usually over before the heart disease becomes clinically apparent, so that the throat swab, feces, and pleural or pericardial fluid will usually prove to be negative on culture.

Unlike neonates, adults with heart involvement will usually recover completely, but residual damage, such as chronic enlargement of the heart, electrocardiographic abnormality, and constrictive pericarditis, may remain. The patient with pericardial pain may be considered to have suffered a myocardial or pulmonary infarction, and anticoagulants may be given with disastrous results.[6]

The mechanism of adult Coxsackie heart disease is not yet clearly understood, but there is suggestive evidence that it is, basically, a hypersensitivity or autoimmune reaction of the type found in postmyocardial infarction syndrome, chest wall trauma, and after heart surgery.[7]

There is no specific therapy, and experimental evidence in adult mice indicates that steroids given at an early stage of the illness may hasten the progress of the myocarditis.[8] This is not to say that steroids given at a *later* stage of the disease might not be life-saving if indeed delayed hypersensitivity plays a major role.

A good index of suspicion is necessary to make the diagnosis, and prolonged study and follow up is essential to delineate the natural history of this interesting disease.

REFERENCES

1. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J., Measroch, V., and Kirsch, Z.: Myocarditis in the newborn infant—A study of an outbreak associated with Coxsackie group B virus infection in a maternity home in Johannesburg, J. Pediat. 48:1, 1956.
2. Smith, W. G.: Adult heart disease due to the Coxsackie virus Group B, Brit. Heart J. 28:204, 1966.
3. Christian, H. A.: Nearly ten decades of interest in idiopathic pericarditis, Am. Heart J. 12:645, 1951.
4. Burch, G. E., and DePasquale, N. P.: Viral endocarditis, (Editorial) Am. Heart J. 67:721, 1964.
5. Rhodes, A. J., and van Rooyen, C. E.: Textbook of virology, ed. 4, Baltimore, 1962, Williams & Wilkins C.
6. Smith, W. G.: Postcardiotomy syndrome, anticoagulants, and haemopericardium, Lancet 1:750, 1961.
7. Sanders, V.: Viral myocarditis, Am. Heart J. 66:707, 1963.
8. Kilbourne, E. D., Wilson, G. B., and Perrier, D.: The induction of gross myocardial lesions by Coxsackie (pleurodynia) virus and cortisone, J. Clin. Invest. 35:362, 1956.

Clinical communications

The effect of drug treatment of hypertension on the distribution of deaths from various causes

A study of 173 deaths among hypertensive patients in the years 1959 to 1964 inclusive

J. I. Hodge, M.D., F.R.A.C.P.
F. H. Smirk, K.B.E., M.D., F.R.C.P., F.R.A.C.P.
Dunedin, New Zealand

It is now generally recognized that effective antihypertensive treatment prolongs survival for the majority of hypertensive patients. Comparatively little attention has been paid, however, to the eventual causes of death among such patients. Data published previously from this clinic[1] showed the frequency of individual causes of death in treated patients to differ in several ways from that in an earlier group of untreated hypertensive patients. A subsequent report emphasized changes in the pattern of deaths among treated hypertensive patients in the years 1959, 1960, and 1961. The changes which were apparent in the treated group prior to 1959 were a fall in the percentage of deaths due to heart failure and stroke and a rise in the percentage of uremic deaths; there was little change in the percentage of deaths from coronary artery disease. Between 1959 and 1961, with a further fall in the annual death rate for this population of treated hypertensive patients, a new trend emerged, namely, a marked rise in the percentage of deaths from definite or presumptive coronary artery disease. Recently this cause has been found to predominate in both sexes, whether evidence of ischemic heart disease had or had not been present at the outset of treatment, and irrespective of the particular regimen of treatment used. The aim of the present paper is to examine in detail all deaths which have occurred among hypertensive patients treated at the Dunedin clinic in the 6 years 1959-1964. Apart from the incorporation of new drugs into the treatment regimen, there have been no major changes in our management of hypertensive patients, and a valid comparison can be made, therefore, with the series of deaths reported in earlier publications.

Material and methods

The 173 deaths analyzed in this paper are those of patients who attended the Dunedin Hospital hypertension clinic for treatment and who died between the dates Jan. 1, 1959, and Dec. 31, 1964. All patients had been investigated fully on first being referred to the clinic and had been established on antihypertensive treatment for varying periods before death. The treatment regimen was arranged to

From the Wellcome Medical Research Institute, University of Otago Medical School, Dunedin, New Zealand.
This work was carried out under grants from the Medical Research Council of New Zealand.
Received for publication March 20, 1964.
Address: Wellcome Medical Research Institute, University of Otago Medical School, P.O. Box 913, Great King St., Dunedin, C.1, New Zealand.

suit the individual patient and therefore varied considerably. Regular supervision including all-day tests of blood pressure when necessary was continued in so far as possible for all patients, and deaths were classified as occurring "while on treatment" by the same criteria as reported previously.[2]

All the patients under treatment for hypertension at our clinic during the 6-year period were at risk of dying while on treatment and thus qualifying for inclusion in the analysis. As with the patients who died, all patients at risk were fully investigated when first seen at the clinic and the diagnosis by exclusion for the great majority was essential hypertension. The retinal grading used has been that of Keith, Wagener, and Barker[4] and the figures given throughout this paper for both age and retinal grade are those immediately before the start of treatment with the clinic.

In a number of cases there were two major factors which appeared to contribute equally as causes of death, and in this analysis, as with the earlier ones, such deaths have been treated by allocating a half mark to each contributing factor, for example, uremia ½, heart failure ½. The figures shown for individual causes of death, therefore, represent the sum of whole marks allocated to patients dying solely from that cause and half marks for patients in whose death another cause was also operative. Fractions in the numbers shown for individual causes of death are explained on this basis. This method of classification may be illustrated from Table II. The number of individual causes of death shown in the category *Sudden cardiac* (11½) represents 13 patients contributing 10 whole and 3 half causes; similarly, the 39 causes of death from stroke represent 44 patients contributing 34 whole and 10 half causes. The over-all total of these numbers must, of course, correspond to the total number of deaths.

The cause of death was clear in most cases from the clinical and other evidence available. Confirmation by autopsy was possible only when death occurred in the hospital and was obtained for 53 of the patients (30.6 per cent). The categories used for classification of deaths are the same as those used in previous similar publications.

Results

The Dunedin hypertension clinic has maintained a steady rate of growth during the period under study (Fig. 1), with the result that the population at risk increased from 413 at the beginning to 726 at the end of the 6-year period. The distribution of the patients according to the severity of retinal changes is shown in Table I, together with average numbers

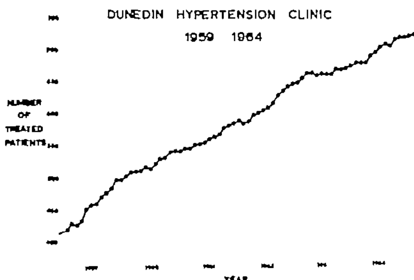


Fig. 1. Rate of growth of the hypertension clinic of the Dunedin Hospital, 1959-1964.

based on the situation at the beginning and at the end of the period. These have been used in the calculation of over-all annual mortality which is discussed later. The major emphasis of this paper, however, is on the *percentages* of deaths due to various causes among patients dying while on antihypertensive treatment and not on the total number of deaths in relation to clinic population.

Table II shows the causes of death for the 173 patients who died during 1959-1964; these were grouped according to the severity of retinal changes.

The term *Sudden cardiac* refers to unexpected deaths in which the previous history and/or mode of dying gave a strong suspicion of a cardiac origin, probably but not proved to be due to underlying coronary artery disease. Most of these deaths were instantaneous and occurred without any prior warning; the majority happened away from the hospital so that additional evidence from autopsy was usually lacking. Sudden deaths for which there was definite evidence of associated myocardial infarction are included in the *Coronary* category. The table shows that definite or strongly presumptive coronary artery disease is the predominant cause of death in hypertensive patients with retinal grades 1, 2, and 3, and is easily the most important cause when all grades are combined. Trends within the 6-year period are not shown in Table II, but it is noteworthy that a considerable rise occurred in the percentage of deaths from causes unrelated to hypertension (10.4 per cent in 1959-1961 and 24.2 per cent in 1962-1964). This is presumably the result of a further reduction in deaths due directly to complications of untreated hypertension. When such deaths due to unrelated causes are excluded, the percentage of coronary and sudden deaths becomes 50.9 per cent, i.e., *for treated hypertensive patients approximately half the deaths related to the hypertension have been due to definite or presumptive coronary artery disease.* There were 3 whole and 15

Table I. Average numbers of patients attending the Dunedin Hospital hypertension clinic from 1959 to 1964 inclusive, together with the total deaths during this period

	Retinal grade					Total
	1	2	3	4	?	
Patients "at risk" on Jan. 1, 1959						
Male	24	63	34	12	0	133
Female	55	148	66	11	0	280
Combined	79	211	100	23	0	413
Patients "at risk" on Jan. 1, 1965						
Male	97	112	38	10	3	260
Female	183	201	66	11	5	466
Combined	280	313	104	21	8	726
Average numbers at risk, 1959-1964 inclusive						
Male	60.5	87.5	36.0	11.0	1.5	196.5
Female	119.0	174.5	66.0	11.0	2.5	373.0
Combined	179.5	262.0	102.0	22.0	4.0	569.5
Total deaths, 6-year period						
Male	15	40	23	8	1	87
Female	16	42	24	3	1	86
Combined	31	82	47	11	2	173

Table II. Distribution of causes of death according to retinal grade

Cause of death	Retinal grade 1		2		3		4		?		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Coronary	13	42 0	29	35 4	16	34 0	3	27 3	0	0	61	35 3
Sudden cardiac	1	3 2	7	8 5	3	6 4	½	4 5	0	0	11½	6 7
Stroke	6½	21 0	23	28 0	8½	18 1	1	9 1	0	0	39	22 5
Uremia	2½	8 1	3	3 7	7	14 9	3½	31 8	½	25	16½	9 5
Congestive heart failure	2	6 4	5	6 1	3	6 4	½	4 5	0	0	10½	6 1
Other relevant	0	0	1	1 2	2	4 2	1	9 1	0	0	4	2 3
Other unrelated	6	19 3	14	17 1	7½	16 0	1½	13 7	1½	75	30½	17 6
Total	31	100 0	82	100 0	47	100 0	11	100 0	2	100	173	100 0

part causes of death (6.1 per cent) contributed by congestive heart failure. This is considerably lower than the figure of 23 2 per cent reported by Hodge McQueen and Smirk for untreated hypertensive patients

Four deaths are listed as *Other relevant* Two patients died after rupture of a dissecting aneurysm of the aorta one having sustained his first aortic dissection with hemiplegia 6 years before death Two deaths were suicides in patients on treatment with reserpine. The *Unrelated* causes of death include malignant disease (10 whole 4 part causes) diabetes (4 part causes) pneumonia (4 part causes) obstructive lung disease (2 whole 2 part causes) bronchial asthma (3 part causes) motor accident (2 whole causes) and one whole cause each for status epilepticus, suicide postoperative pelvic abscess, postoperative pulmonary embolus, and hepatic cirrhosis. Part causes of death were also contributed by a small bowel infarct resistant anemia fractured neck of femur postoperative complications after amputation volvulus, and tuberculosis. A patient with bacterial endocarditis developed a severe depression leading to suicide (the case included in the above list) he was not under treatment with any drugs known to induce a depressive state and his personality change was thought to be due to multiple cerebral emboli of cardiac origin

Relationship of casual and basal blood pressure at the start of treatment to cause of death. The blood pressure levels before treatment provided a further guide to the severity of hypertension in the 173 patients who died An analysis of the blood pressure at first examination in relation to cause of death is shown in Tables III IV The lowest average blood pressures were in the group in which death was due to definite coronary artery disease. For this group the casual systolic pressure was significantly lower than that for all deaths ($0 01 > p > 0 001$) and lower than that for the separate categories of *Stroke* and *Sudden cardiac* ($p > 0 001$) The casual diastolic pressure was lower than that for the categories of *Stroke* ($0 05 > p > 0 02$) *Sudden cardiac* ($0 01 > p > 0 001$) *Uremia* ($0 05 > p > 0 02$) and *Other relevant* ($0 02 > p > 0 01$) A similar pattern was shown by the basal blood pressures for the *Coronary* group which were significantly lower than those for all other categories of death except *Other unrelated* (systolic and diastolic) and *Sudden cardiac* (diastolic only) These changes were not attributable to the presence of coronary artery disease before the start of treatment (average basal blood pressure of patients with coronary artery disease before treatment 165 3/98 9 mm Hg average of patients with no previous coronary disease 163.2/98 0 mm Hg)

Table III *Relationship of casual and basal blood pressures before treatment to the cause of death*

Cause of death	Average B.P. (casual) before treatment (mm. Hg)		Average B.P. (basal) before treatment (mm. Hg)	
	Number	B.P. (± S.D.)	Number	B.P. (± S.D.)
Coronary	61	213 4 (± 28 8) / 121 3 (± 18 0)	55½	163 6 (± 24 4) / 98 1 (± 15 4)
Sudden cardiac	11½	238 4 (± 25 1) / 132 6 (± 14 7)	10½	179 3 (± 30 7) / 103 0 (± 26 8)
Stroke	39	228 4 (± 27 7) / 127 4 (± 21 6)	33½	179 2 (± 22 0) / 105 6 (± 14 6)
Uremia	16½	223 5 (± 20 7) / 129 4 (± 16 7)	12½	178 2 (± 22 5) / 108 1 (± 17 4)
Congestive heart failure	10½	220 0 (± 27 4) / 123 9 (± 14 3)	8½	179 2 (± 22 5) / 108 1 (± 13 1)
Other relevant	4	230 0 (± 16 5) / 137 5 (± 15 8)	4	184 0 (± 6 6) / 122 0 (± 7 9)
Other unrelated	30½	2[illegible]1 7 (± 32 4) / 123 5 (± 18 7)	23½	164 7 (± 26 2) / 98 3 (± 17 8)
All deaths	173	221 7 (± 28 8) / 125 1 (± 18 7)	148	171 1 (± 25 1) / 102 2 (± 17 2)

Basal blood pressure not recorded in 25 cases.

The group of deaths from stroke was the only category in which the average basal systolic pressure was significantly *above* that for the whole series, and the *Sudden cardiac* deaths were the only group to show a similar change in casual systolic blood pressures.

Patients who ultimately died of coronary disease thus showed a rather lower average level of blood pressure at the start of treatment and higher average levels were found among patients who died from stroke. However for both groups there was a wide overlap of individual observations with those of patients dying from other causes. The cause of death in a treated hypertensive patient must obviously be influenced by factors other than the initial blood pressure level and some of these will now be examined.

Relationship of starting age and duration of survival to cause of death. The age decade in which patients were started on treatment is related to the final causes of death in Table V. The average age at the start of treatment for the whole group was 55 6 years, and this showed no variation between the first and second halves of the study period.

It can be seen from Table V that *Coronary* plus *Sudden cardiac* causes were the predominant causes of death in all age groups studied. Sixty-one patients (35.3 per cent of those who died while on treat-

Table IV Casual and basal blood pressure (mm. Hg) recorded before the start of clinic treatment showing distribution according to cause of death

Cause of death	Casual blood pressure: Systolic <150	150-169	170-189	190-209	210-229	230-249	250-269	270+	Total	Diastolic <90	90-99	100-109	110-119	120-129	130-139	140-149	150+	Total
Coronary		2½	8½	16	15	11½	3½	4	61	½	2	7	15	17½	10	5½	3½	61
Sudden cardiac				1	1½	4½	2	2	11½				1½	2	3	3½	1½	11½
Stroke		½	2½	3½	14½	7	7½	3½	39		4½	4	3½	8	6½	5	7½	39
Uremia				3½	5	3	2½	½	16½			3	4	2	3	4	2½	16½
Congestive heart failure			1	3½	2	2½	½	1	10½				3½	4½	½	½	1½	10½
Other relevant					2	1	1		4					1	1	1	1	4
Other unrelated		2	3	4	8	6½	3	4	30½	½	1½	4½	7	6	2	4½	4½	30½
Total		5	15	32	48	38	20	15	173	1	8	16	35	41	26	24	22	173

Cause of death	Basal blood pressure: Systolic <140	140-149	150-159	160-169	170-179	180-189	190-199	200+	Total	Diastolic <80	80-89	90-99	100-109	110-119	120-129	130-139	140+	Total
Coronary	10½	4½	4½	7½	12	9	6	1½	55½	4	9½	20½	8½	6	5½	½	1	55½
Sudden cardiac		1	2	3½			1	3	10½	1	1	4	2	1		½	1	10½
Stroke	2½		2	7	5	4	6½	6½	33½	½	4	7	8½	8½	3	1	1	33½
Uremia		2		2	3	2	2	1½	12½	1	1½	1½	2½	3	2		1	12½
Congestive heart failure	½	½	½	1½	1	½	3	1	8½		½	2	2	2	1½	½		8½
Other relevant					1	1	2		4					1	2	1		4
Other unrelated	4½	5	1	4½	1	2½	1½	3½	23½	2½	4½	7	2½	3½	2	½	1	23½
Total	18	13	10	26	23	19	22	17	148	9	21	42	26	25	16	4	5	148

Basal blood pressure not recorded in 25 cases.

Table V Causes of death related to age at start of clinical treatment

Cause of death	Age at start of treatment (yr)					Total	
	70+	60-69	50-59	40-49	<40	Number	Per cent
Coronary	2½	20½	20	13½	4½	61	35 3
Sudden cardiac	1	5½	2	2	1	11½	6 7
Stroke	—	12	16½	10½	—	39	22 5
Uremia	—	3½	7	4½	1½	16½	9 5
Congestive heart failure	—	3½	5½	1½	—	10 ½	6 1
Other relevant	—	—	3	1	—	4	2 3
Other unrelated	1½	11	11	6	1	30½	17 6
Total	5	56	65	39	8	173	100 0

Table VI Duration of survival for patients dying from various causes

Cause of death	Number of years of survival											Total
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10+	
Males												
Coronary and sudden cardiac	5	2	5	4½	7½	½	1	4	—	3½	6	39
Stroke	3	2½	1	1	—	2	½	2½	1	—	—	13½
Uremia	5½	3½	—	1	1	2½	—	1	—	—	—	14
Congestive heart failure	1½	1½	—	½	½	1	—	½	—	1	—	6
Other relevant	—	1	—	—	1	—	—	—	1	—	—	3
Other unrelated	5	1½	—	1	—	1		1	1	—	—	11
Total	20	1	6	8	10	7	2	9	3	4	6	87
Females												
Coronary and sudden cardiac	3	2½	2	4	3	2	5	5	4			33
Stroke	2	1½	1½	2	3	2½	3	3	—	2	5	25
Uremia	1½	—	—	—		—	—	—	—	—	—	2
Congestive heart failure	½	½	1	1½	—	½	—		—	—		4
Other relevant	—	—	—	—	—	—	—	—	1	—	—	1
Other unrelated	2	1	3½	2½	2½	2	—	1	2	1		19
Total	10	6	8	10	9	7	8	10	7	5	6	86
Grand total	30	18	14	18	19	14	10	19	10	9	1	173

ment) were 60 years old or older at the time of starting treatment. At the time of death 98 patients (5 per cent) were 60 years old or older, 27 being over the age of 70 whereas only 47 patients (27 per cent) were under 50 years of age. This age bias is to be expected since the greatest number of new hypertensive patients are taken on for treatment in the sixth decade of life and many a considerably older. The continued aging of the hypertensive population will obviously limit the extent to which annual mortality figures can fall in response to effective treatment.

The duration of survival on treatment for all patients dying in the years 1959 to 1964 is related to the separate causes of death in Table VI.

Of the 87 males who died in this period 31 (35 6 per cent) survived more than 5 years from the outset of treatment 43 of the 86 females who died (50 0 per cent) survived longer than 5 years from the date of starting treatment. For both sexes combined the 5 year survival among patients who died was 42 8 per cent. It is noteworthy that the average duration of survival for males (but not females) in the *Coronary* and *Sudden cardiac* categories has increased being 4 7 years in 1959-1961 and 5 8 years in 1962 1964 For the whole group of patients who died the average time of survival from the start of clinic treatment was 4 7 years.

The change which has taken place in the distribution of the causes of death in association with treatment is set out in Table XII Although it is recognized that different series even of untreated patients may have a somewhat different distribution of causes of death the differences which have developed in association with hypotensive therapy are of a striking character

It is reasonable to suppose that the cause of death for any patient would be influenced considerably by the presence or absence of vascular complications of hypertension (coronary disease heart failure stroke) during life The effect of these disabilities will now be considered

Effect on the causes of death of the presence or absence of definite or suspected coronary disease at the start of treatment In order to determine whether the high mortality rate from coronary artery disease was due to the number of patients in whom this condition was established prior to treatment, the 1959-1964 deaths have been analyzed further The following points have emerged

(a) Forty-eight patients presented originally with evidence of coronary disease (*angina pectoris or previous infarction*) in these 76.5 deaths (55 2 per cent) were due wholly or in part to coronary disease

(b) One hundred and twenty five patients who died had no *evidence* of coronary disease at the start of treatment In this group coronary disease or sudden death was the cause of 39½ deaths (31 6 per cent) When causes unrelated to hypertension are excluded coronary disease together with sudden cardiac death is the *most common cause of death in this group* (40 1 per cent) Stroke is the next most frequent cause (24 9 per cent)

(c) It is clear then that coronary deaths are more likely to occur in patients who have shown previous evidence of coronary disease however this still remains the most important cause of death among patients with no such previous evidence

(d) Angina pectoris developed in some patients in the course of treatment with antihypertensive drugs, and the total

Table XII Percentage distribution of deaths among untreated and treated hypertensive patients

	Old untreated series	*Untreated 1950-1958†*	*Treated 1950-1958†*	*Treated 1959-1964*
Coronary Sudden cardiac	21 4	17 1	19 2	42 0
Stroke	32 0	39 6	33 1	22 5
Uremia	1 4	12 2	20 5	9 5
Congestive heart failure	21 7	23 2	12 7	6 1
Other relevant Other unrelated	23 5	7 9	14 6	19 9 (2 3) (17 6)
Total number on which percentages are based	175	8	151	173

*Figures from follow-up of patients referred to by Smirk and associates
†Hodge and associates.

number exhibiting this symptom prior to death is, therefore, greater than shown in (a) above. For example in the years 1962 1964 39 hypertensive patients died in whole or part from coronary causes, and 28 (72 per cent) of these had angina for an average of 4.3 years before death By comparison in a group of 72 consecutive normotensive patients who died in the Dunedin Hospital from myocardial infarction only 33 (46 per cent) gave a history of angina the average duration being 4.9 years. The symptom occurred much less frequently among the other 52 hypertensive patients who died of other causes only 10 of these (19 per cent) had angina, for which the average duration in this group was 4.7 years.

Effect on the causes of death of heart failure at the start of treatment Among 38 patients presenting with left ventricular or congestive heart failure but without evidence of coronary disease who died only 5 deaths (13.2 per cent) were attributable to heart failure whereas 8 deaths (21.1 per cent) were attributed to coronary disease and 7 others (18.4 per cent) were sudden cardiac deaths without other evidence suggesting coronary disease thus, coronary and sudden deaths combined accounted for 15 deaths (39.5 per cent) Seven and one half deaths (19.7 per cent) were attributed to stroke.

Among 87 patients with neither heart failure nor evidence of coronary disease at the outset, 3½ (4.0 per cent) deaths could be attributed to heart failure whereas 23½ deaths (27.0 per cent) were due to coronary disease and an additional 6½ were sudden coronary and sudden deaths combined thus accounted for 30 deaths (34.5 per cent) Stroke accounted for 19 deaths (21.8 per cent)

Sixty-seven of the patients who died in the years 1962 1964 started clinic treatment with no evidence of coronary artery disease but of these — were in cardiac failure However coronary deaths were no more frequent among the group presenting with heart failure but no manifest coronary disease (6 causes, 27 per cent) than among those 45 patients who had neither disability at the start of treatment (1 ½ causes 28 per cent) *This observation strengthens the findings reported previously and indicates that occult coronary disease was probably not an important factor in the occurrence of heart failure prior to antihypertensive treatment* It is rare for heart failure to be the sole cause of death in adequately treated hypertensive patients in all except one of our cases, another factor e.g valvular heart disease provided an explanation of persistent heart failure.

Effect on the causes of death of stroke at the start of treatment Fifty patients who died during 1959 1964 presented originally with a history of major or minor stroke but showed no evidence of coronary artery disease. In this group 17 causes of death (34 per cent) were contributed by coronary disease and 12½ (25 per cent) by further stroke.

Sixty-eight patients presented originally with no evidence of either previous stroke or coronary diseases In 26 of these (38 per cent) death was due to coronary disease and in 15 (22 per cent) to stroke

Thus the importance of coronary disease as a cause of death is emphasized by this group also Even among those patients who were especially at risk of dying from stroke—those who had sustained a major stroke prior to treatment—coronary causes still predominated

Over-all annual mortality in relation to retinal grade at the start of treatment As mentioned above the average annual mortality for the 6-year period has been obtained by expressing total deaths per year as a percentage of the average population at risk. For all retinal grades combined the death rate was 5.1 per cent per annum the rate was lower for females (3.8 per cent) than for males (7.4 per cent) As expected increased severity of retinal grading coincided with increased mortality rate, the figures for male and female patients combined being Grade 1 2.9 per cent per annum Grade 2 5.2 per cent Grade 3 7.7 per cent and Grade 4 8.3 per cent

Discussion

The over-all improvement in life expectancy for hypertensive patients on effective treatment is now well documented and needs no emphasis here A small additional fall in the annual mortality for such patients has been observed in our

clinic for the years 1962 1963 and 1964 when compared with the previous 3 years, but it seems to be unreasonable to expect that this trend will continue

It has become evident that a reduction in the mortality from causes such as heart failure or stroke leaves a high per cent mortality from definite or suspected coronary artery disease as one of the major challenges to physicians concerned with the management of such patients. Some of the sudden deaths may of course be due to ventricular arrhythmias, either with or without severe coronary disease and recognition of this group during life would provide an important guide to correct therapy Therefore it is desirable that the evidence for involvement of the coronary arteries should be examined critically A difficulty in obtaining this information is that the majority of such deaths occur away from the hospital and autopsy examination s frequently not possible Among the patients who died from coronary or sudden cardiac causes in 1959-1964 autopsy was available for only 16 Nine of these showed recent coronary occlusion and the remainder showed coronary atheroma of varying severity

Because of the need for more accurate classification of such deaths, a further analysis of those classified as *Coron ry* and *Sudden cardiac* is shown in Table VIII It is thought that the use of such a subdivision would facilitate a comparison of results from different clinics. Coronary deaths are shown here as definite highly probable or probable according to the evidence available the latter group (11½ causes) corresponding to the category of *Sudden ca diac* used in earlier tables. Half causes are again used to describe cases in which another factor was deemed to be equally responsible for death for example the first category of 5½ causes actually includes 7 patients contributing 4 whole and 3 half causes. The phrase "apparently cardiac" refers to deaths which were not instantaneous but which were associated with other clinical features indicating a cardiac origin

The question arises whether the increased percentage of coronary deaths among treated hypertensive patients can be related to any major change in drug treatment. The only notable changes in recent years have been the widespread use of the thiazide diuretics and drugs which selectively inhibit orthosympathetic nerve transmission e g bretylium guanethidine bethanidine Of the 39 *Coronary* and *Sudden cardiac* deaths in the last 3 years of the study 29 patients (74 per cent) had been on treatment with thiazides 23 (59 per cent) with guanethidine and/or bethanidine and 3 (7 7 per cent) with alpha methyldopa Corresponding figures for the 52 patients who died from other causes were thiazides 37 (71 per cent) guanethidine and or bethanidine 23 (44 per cent) and alpha methyldopa 8 (15 per cent) Comparison is more difficult for the latter drugs since the decision to use them was influenced by a number of factors including severity undesirability of postural hypotension etc So far as mentioned above no difference has been found between the incidences of coronary death in persons receiving thiazides and in those not receiving them

Although improvements in hypotensive drug therapy may be expected to decrease further the incidence of strokes there is so far no indication that present methods are likely to decrease the proportion or the number of coronary artery deaths. The autopsy study by Smith and associates, of the Mayo Clinic on virtually untreated hypertensive patients showed that among hypertensive patients who died from conditions such as heart failure or stroke about 60 per cent had substantial coronary artery disease This would seem to explain why a reduction by treatment in the number of patients dying from heart failure and stroke is associated with an increase in the proportion who die from coronary disease A relationship between vascular disease in coronary and cerebral arteries has been shown by Mitchell and Schwart In keeping with this finding is the incidence of coronary artery disease contributing to death even among patients in our series with severe cerebrovascular complications at the outset of treatment It is possible that a reduction in the blood pressure might slow the rate of development of coronary artery disease but if so it appears that it would be necessary to reduce the blood pressure at an

Table VIII Further analysis of deaths classified as coron ry or sudden cardiac (see text)

	Number of cases			Number of cases			Number of cases
Definit evidenc of oronary death	17	Either	A topsy evidence of terminal myocardial I f rction or oron ry thrombosis	5½			5½
		or	Clea evidenc li ically of terminal m ocardial infarctio	8½			8½
		or	Both of the abov	3			3
E idence f coronary death highly probable	44	Either	Autopsy evidence of substa tial oronary disease together ith	3½	Either	Sudden death d terminal hest pain	1½
					or	Sudden death, no terminal hest pain	2
					or	Death pparently ardiac nd terminal hest pai	
		or	Clinical evidenc of previous oronary disease such as ngina or myocardial I farction together with	34½	Either	Sudden death nd terminal hest pain	11
					or	Sudden de th no terminal hest pai	21
					or	Death pparently cardiac nd terminal chest pai	2½
		or	N li ical evidence of previous coronary disease together ith	6		Sudden death nd terminal hest pai	6
E idence for oronary death probable	11½	Either	Clinic l evidenc f previous coronary disease together with	1½		De th pparently cardiac terminal chest pain	1½
		or	N linical evidence of previous coronary dise se together w th	10	Either	Sudden death no terminal hest pai	10
					or	Death pparently rdiac and terminal chest pai	0

earlier stage than is usual at the present time

Measures such as a reduction in the blood cholesterol may be applied in the hope of retarding the development of coronary artery disease Of great interest however from the standpoint of reducing the number of coronary deaths among treated hypertensive patients is the high incidence among them of sudden or unexpected death Sudden unexpected death was a more frequent termination than cardia infarction of sufficient duration to allow antemortem diagnosis to be made

We are therefore now attempting to lessen the risk of fatal arrhythmias in high risk patients by the use of the β receptor blocking agents and other antiarrhythmic drugs.

Heart failure as the cause of death is now uncommon among adequately treated hypertensive patients Unsatisfactory treatment however may still be associated with resistant heart failure as shown by 3 patients of this series. In most cases, another explanation for continued heart failure is available The question of adequacy of treatment in relation to duration of survival and cause of death is of considerable importance and is being studied at present.

Summary

An analysis is presented of the 173 deaths which occurred in the years 1959 to 1964 among an average population for the 6 years of 569 treated hypertensive patients

Coronary artery disease together with sudden cardiac deaths probably but not proved to be due to coronary artery disease is now the most important cause of death together accounting for 42 per cent of all deaths or 50 9 per cent of deaths when causes not related to hypertension are excluded Approximately half of all deaths classified as coronary occur suddenly without known premonitory chest pain. In most cases a clear previous history of coronary artery disease is available however it is possible that some are arrhythmic deaths not necessarily due to coronary artery disease The need for more detail in the documentation of such cases is stressed and a fuller classification for future studies is proposed

Cerebrovascular deaths during the years 1959 to 1964 comprised 22 5 per cent of the total deaths, compared with 33 1 per cent in the total of treated patients in the years 1950 to 1958 and 32.0 to 39 6 per cent in two untreated series from our clinic. Taken in conjunction with the reduced over-all mortality in treated persons, these results confirm previous reports that effective treatment decreases the incidence of cerebrovascular deaths.

The percentage of deaths from unrelated causes (e.g malignancy) for 1962 1964 was more than twice that for the previous 3 years reflecting presumably an over-all reduction in deaths due to the vascular complications of hypertension

The mortality rate from all causes (in males and females combined) was 5 1 per cent per annum being lowest for retinal Grade 1 patients (2 9 per cent per annum) and highest for Grade 4 patients (8.3 per cent per annum)

W wish t thank ther physicians in the hypertension clinic and in this city for their cooperation i the management of the patient reported and in deta ling the mod of death i some cases. *Blood* pressure recording by Mrs. G Hobbs nd other tech icians and the provision of a tihypertensiv drugs by various firms are lso acknowledged

REFERENCES

1 Hodge J V McQueen E. G., nd Smirk, F H Results of hypotensive therapy i arterial hypertension, Brit. M J 1 1 1961
2. Smirk, F H nd Hodge, J V Causes of death in treated h pertensive patients, Brit. M J 2 1221 1963.
3. Keith N M Wagener H P and Barker N W Some different types of essential hypertension Their course nd prognosis, *Am. J M Sc* 197 332, 1939
4 Smirk F H Veale, A M O and Alstad, K Basal and supplemental blood pressures in relationship t lif expectancy and hypertension symptomatology New Zealand M J 58 711 1959
5 Smith D E., Odel, H M and Kernohan, J W Causes of death in hypertension Am J Med. 9:516, 1950.
6 Mitchell J R A and Schwartz, C. J : Relationship between arterial disease i different ites, Brit M J 1 1293 1962

Electrocardiographic characteristics of P pulmonale waves of coronary origin

Desiderio Gross, M.D.
Santiago, Chile

The morphologic type of P pulmonale wave is recognized as a well-defined form of the atrial wave that may have a different origin. Peaked tall nonwidened P waves in Leads II, III, aV, usually associated with a marked P T wave and deviation of the electrical axis to the right in the frontal plane, assuming an almost vertical position, are the leading features of this type of P wave. It is most frequently observed (a) in patients with cor pulmonale of any origin, (b) in healthy subjects with asthenic body build, and (c) in patients with coronary pathology, generally with signs and symptoms of angina pectoris and myocardial infarction.

Although early changes in the ventricular complex of the electrocardiogram due to disturbances in the coronary circulation are well recognized, observations concerning concomitant changes in the morphologic aspects of the atrial wave have been few. As early as 1933 Master[1] described enlarged widened P waves in cases of myocardial infarction. He regarded these as being due to the burden of heart failure upon the atrial cavities, causing dilatation of them, and found that these P waves may disappear when the cardiac condition improves. Wood and Wolferth reported huge T waves in the precordial leads in the healing stages of myocardial infarction. Dressler and Roesler[3] observed that the earliest sign of coronary occlusion, 1 hour after the onset of the symptoms, was the appearance of huge T waves in the precordial leads. Freundlich investigated minutely the presence of large upright T waves in the precordial leads of 110 patients with coronary heart disease complaining of anginal pain on exertion and concluded that the presence of huge T waves is a diagnostic sign of damaged myocardium.

All of these authors referred exclusively to changes in the ventricular complex provoked by impairment of the coronary circulation; little attention has been paid to any eventual changes in the atrial wave which might have been present simultaneously. In his paper Freundlich reports (Figure 14) the case of a 58-year-old man who had been suffering severe attacks of angina pectoris on exertion for 3 months. At first, the electrocardiogram was normal, although high T waves were present in Precordial Leads V and V$_2$. The P wave in Lead I was 1.1 mm in height; in Lead II it was flattened almost isoelectric, and in Lead III it measured 1.2 mm. A week later there were signs of acute anteroseptal infarction; the R T segment was elevated in Leads V-V; the P wave was flattened in Lead I, whereas it was tall, peaked, and had a height of 2.5 mm and a duration of 0.10 sec. in Lead II, and remained practically unaltered in Lead III. Consequently, in this case acute myocardial infarction caused characteristic changes in the ventricular complex together with alterations in the atrial wave.

Received for publication May 23, 1966.
Address: Casilla 3076, Santiago, Chile.

In this paper we endeavor to establish the basic linear and angular magnitudes of these waves which simulate P pulmonale waves but are really of coronary origin

Methods and material

Electrocardiograms were inscribed with the patient in the supine decubitus position Three standard leads three unipolar extremity leads and the six unipolar precordial leads were recorded The height and duration of the P wave were measured in the three standard leads and the surface area was calculated The atrial repolarization wave (P T) was observed and its depth estimated The minimal visible P T depression was estimated at 0.2 mm The length of the P R interval was measured whereas the length of the P R segment was calculated by substraction of the duration of the P wave from the length of the P R interval The ratio of the duration of the P wave to the duration of the P R segment (P PR ratio) i e the Macruz index was calculated in each observation The magnitudes of the angles of the P wave were measured *alpha* the angle that the ascending limb of the P wave forms with the base line and *beta* the angle that the descending limb of the P wave forms with the base line And the magnitude of the apex angle *gamma* was calculated using the equation $\gamma = 180^\circ - (\alpha + \beta)$

Thirty patients complaining of chest pain angina pectoris in nature and mostly on exertion were examined 7 patients had electrocardiographic signs of old myocardial infarction 1 had right bundle branch block and 4 were hypertensive In nearly every case the resting electrocardiogram showed abnormal T waves and a depressed S-T segment in Lead I and eventually in Leads V_5-V_6.

Results

Table I shows the mean values with the standard deviations and the ranges of all observations. The mean position of the electrical axis of the P wave ÂP in the frontal plane was located at 60.8 ± 8.8 degrees (45 to 83 degrees) In Lead II the P wave had a mean height of 1.87 ± 0.33 mm (1.4 to 3.0 mm) a mean duration of 0.103 ± 0.013 sec (0.07 to 0.12 sec) and a mean surface area of 9.73 ± 2.40 μv (4.9 to 18.0 μv) The atrial repolarization wave P T was present in Lead II in 80 per cent. The calculated average depth of the P T wave measured 0.27 ± 0.21 mm (0 to 0.8 mm) in this lead The Macruz index was on an average 1.93 ± 0.74 (0.71 to 3.66) indicating left

Table I Linear and angular magnitudes of P pulmonale waves of coronary origin

	ÂP (degrees)	Height (mm)	Duration (sec)	Surface area (μv)	P T (mm)	P R interval (sec)	P R segment (sec)	Macruz index	α (degrees)	β (degrees)	γ (degrees)
I											
Mean		1.12	0.081	4.59	0.09	0.150	0.069	1.32	50.0	60.9	69.1
S.D		±0.33	±0.018	±1.69	±0.12	±0.0[illegible]8	±0.023	±0.58	±12.9	±11.5	±17.9
Min.		0.4	0.03	1.2	0	0.12	0.04	0.35	27	37	35
Max.		1.8	0.12	7.2	0.4	0.20	0.16	3.00	82	87	110
II											
Mean	60.8	1.87	0.103	9.73	0.27	0.164	0.06	1.91	57.73	67.73	54.57
S.D	±8.8	±0.33	±0.013	±2.40	±0.21	±0.0[illegible]4	±0.0[illegible]	±0.74	±8.4	±7.8	±13.3
Min.	45.0	1.4	0.07	4.9	0	0.14	0.3	0.71	40	56	31
Max.	83.0	3.0	0.12	18.0	0.8	0.24	0.14	3.66	80	80	78
III											
Mean		1.09	0.093	4.97	0.09	0.164	0.071	1.93	46.6	47.6	85.8
S.D		±0.35	±0.021	±2.24	±0.01	±0.0[illegible]3	±0.030	±1.12	±14.7	±12.9	±31.2
Min.		0.2	0.04	0.8	0	0.12	0.01	0.22	15	23	[illegible]
Max.		1.8	0.16	9.1	0.4	0.24	0.12	5.00	81	77	125

atrial enlargement. The atrial triangle in Lead II presented a somewhat slowly ascending limb that formed with the base line the angle alpha having an average magnitude of 37.73 ± 9.4 degrees (40 to 80 degrees) and a more perpendicular descending limb that formed with the base line the angle beta having an average magnitude of 67.73 ± 7.8 degrees (56 to 80 degrees). The apex of the P wave represented by the angle gamma was 54.53 ± 12.3 degrees (31 to 78 degrees) on an average.

Discussion

P waves of increased height, normal duration, and with an electrical axis deviated to the right in the frontal plane were observed in cardiac patients who suffered from angina pectoris. These atrial waves displaying the morphologic characteristics of P pulmonale waves were found in coronary patients in whom there was complete absence of any pulmonary pathology such as emphysema, chronic bronchitis, pulmonary hypertension, etc., that may overload the right atrium. Thus, P pulmonale of coronary origin as a distinct electrocardiographic entity seems to be justified. As a matter of fact, Scheuer and associates[8] in studying the atrial vectorcardiogram have observed that in cases of coronary heart disease the P loop may have abnormal duration, orientation, and configuration and may resemble that of atrial enlargement. On the other hand, Chou and Helm, commenting on the nonspecificity of the electrocardiographic pattern of P pulmonale which they call pseudo-P pulmonale, state that, among 100 cases, 3 were of coronary origin. In their experience 36 patients with a pattern of P pulmonale had left rather than right atrial enlargement.

According to Chevalier and Thaon, the normal ÂP in the frontal plane is situated at 49 degrees. The most frequent location according to van Dooren and associates is at 55 degrees and according to Lepeschkin at 60 to 62 degrees.

The electrical axis of the P wave in the frontal plane in cases of P pulmonale is shifted to the right. Novelo[3] considers the average position of the ÂP in this case to be at 64 degrees, and similarly, Burch and DePasquale[11] place it at 64 ± 16 degrees. We found the mean position of the ÂP at 60.8 ± 8.8 degrees (45 to 83 degrees) in the group of coronary patients exhibiting the P pulmonale pattern. When compared with the normal position, this shows a rightward deviation that almost equals the average position of ÂP in patients with true P pulmonale.

The height of the P wave in Leads II and III in the presence of P pulmonale is markedly increased. Burch and DePasquale[11] report 1.39 ± 0.40 mm (0.73 to 2.10 mm), Zuckerman and associates[13] 1.9 mm (0.87 to 3.7 mm), Gross,[14] 1.92 ± 0.54 mm (1.2 to 3.0 mm). The mean height of the P wave found in Lead II in our coronary patients exhibiting the P pulmonale pattern was 1.87 ± 0.33 mm (1.4 to 3.0 mm), i.e., nearly as high as most authorities describe in cases of true P pulmonale.

We found that the average duration of the P waves of pulmonary type of coronary origin was 0.103 ± 0.013 sec. (0.07 to 0.12 sec.), i.e., lying entirely within normal limits according to published experiences.

The surface area of the P waves of coronary origin in Lead II is definitely enlarged; we found an average area of 9.73 μvs ± 2.40 (4.9 to 18.0 μvs)—62.9 per cent larger than the normal. Similar figures were observed in measurements of the surface area in patients with P pulmonale, i.e., 10.5 μvs ± 2.93 (6.4 to 15.6 μvs) on an average. Burch and DePasquale[11] observed an average magnitude of 6.11 ± 1.88 μvs for the normal surface area of the P wave in Lead II and an almost equal figure of 6.6 μvs ± 2.24 for the P pulmonale wave. In our experience the surface area of the P pulmonale wave and that of the P pulmonale wave of coronary origin are both enlarged in nearly equal proportion when compared with the normal values.

The atrial repolarization wave (T_P) was present in Lead II in 80 per cent, exhibiting an average depth of 0.27 ± 0.21 mm (0 to 0.8 mm). Burch and DePasquale[11] report the presence of a visible P-T wave in as many as 50 per cent of the cases with cor pulmonale, and Wasserburger and associates[8] indicate the presence of a markedly deep atrial repolarization wave of 1.0 mm or even more in cases of emphysema. We

may conclude therefore that the atrial repolarization wave in cases of P pulmonale of coronary origin although more frequently observed than in cases of true P pulmonale, is not so deep as in this latter group

The P PR ratio according to Macruz and associates[14] expresses briefly the type of atrial enlargement. In patients with normal atria the Macruz index ranges from 1 0 to 1 6 when right atrial enlargement is present the index is smaller than 1 0 and with left atrial enlargement it is greater than 1 6. This procedure has been widely investigated by different authors (Kahn and associates [1] Gross [7] Pipberger and Tanenbaum) in general with unsatisfactory results. On the basis of our detailed study we have concluded that the expression *P PR* has no exact significance and that it is not related to atrial volumes. In our present study its average magnitude was 1 93 ± 0 74 (0 71 to 3 66) indicating left atrial enlargement for the whole group However the distribution of the ratios in the different leads (Table II) revealed a contradictory situation in Lead II they were observed in 36.6 per cent of the cases of right atrial enlargement in 40 0 per cent of those of normal atrial condition and in 23 4 per cent of those of left atrial enlargement. Similar conclusions can be drawn from the observations of Burch and DePasquale who found in healthy persons an average Macruz index of 2 19 ± 0 77 indicating left atrial enlargement for the whole group and in the group of patients with cor pulmonale the Macruz index was 2.39 ± 1 33 suggesting marked left atrial enlargement in evident opposition to the actually existing condition of right atrial enlargement necessarily present in this pathologic condition. We may assume therefore that the predictions based on the P PR ratio with respect to the atrial volumes yield no useful information of practical value and may be misleading

The angular structure of the P pulmonale wave of coronary origin closely resembles the true P pulmonale wave (Fig 1) The ascending limb of the P wave of coronary origin presents an angle of elevation angle alpha of 57 73 ± 8 4 degrees, and a more abrupt angle of descent angle beta of 67 73 ± 7 8 degrees. The apex of the atrial triangle is formed by the angle gamma of 54 53 ± 12.3 degrees. The true P pulmonale wave has a somewhat smoother ascending limb of 60 7 ± 8.7 degrees but an identical descending limb with an angle of 67 3 ± 6.0 degrees and an almost equally peaked apex with an angle gamma of 52.0 ± 11 5 degrees. The almost identical angular structure of these two P waves of different origin explains the similarity of their appearance.

The influence of impaired coronary circulation on the ventricular complex of the electrocardiogram is clearly established The earliest alterations pertain to the T waves that appear with increased height in the precordial leads giant positive T waves or asphyxia T waves as a response of the ventricular myocardium to the state of hypoxemia probably mediated by changes in the distribution of intracellular and extracellular potassium Therefore the

Table II Distribution of P PR ratios in cases of P pulmonale waves of coronary origin

	Macruz index		
	Right atrial enlargement ( )	*Normal condition* (%)	*Left atrial enlargement* (%)
P	13	20	67
P	36 6	40	23 4
P	33 3	40	26 7

giant positive T waves imply a condition of hypoxemia of the ventricular muscle. Tall peaked P waves that appear simultaneously with giant positive T waves in the precordial leads must be interpreted as being equivalent manifestations of hypoxemia of the atrial musculature (Figs. 2 and 3). Hypoxia is one of the most important factors in producing tall peaked P waves. According to Martins de Oliveira and Zimmerman and Chou and Helm[4] arterial oxygen desaturation increases the height of the P wave. Lepeschkin[7] states that the height of the P wave decreases after the patient has inhaled oxygen. We have introduced breath holding as a diagnostic procedure an anoxemic test[24] to elicit further electrocardiographic evidence of coronary insufficiency. After establishing the maximal duration of inspiratory apnea, the second lead *is registered in the last 10* seconds of the respiratory pause. Com

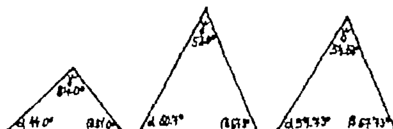


Fig. 1. The angular magnitudes of the normal P wave (*left*), of the true P pulmonale wave (*center*), and of the P pulmonale wave of coronary origin (*right*) in Lead II.

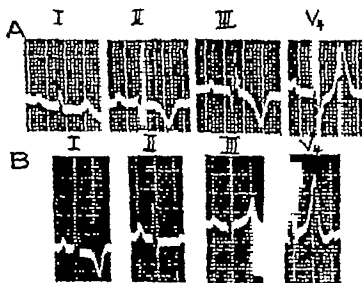


Fig. 2. *Case A.* Male patient, 48 years of age, who 3 months previously had suffered an acute myocardial infarction of posterior localization. Present in Leads II and III are small Q waves and deeply inverted, symmetrical T waves. As an expression of existing hypoxemia, tall, giant positive T wave, 12 mm. in height, can be observed in Precordial Lead V. At the same time, there are tall, peaked P waves, 1.8 mm. in height in Lead II and 1.6 mm. in height in Lead III, concomitant alterations of the atrial ... The P-R interval is prolonged 0.24 sec. in duration. *Case B.* Male patient, 44 years of age, with hypertensive heart disease (blood pressure, 260/160 mm. Hg), complaining of frequent attacks of chest pain that was angina pectoris in nature. The heart shadow is markedly enlarged on fluoroscopic examination. The resting electrocardiogram reveals left ventricular strain pattern in the standard leads, and tall peaked T wave 16 mm. in height, in Precordial Lead V. The P wave is tall and peaked, 2.2 mm. in height, in Lead II and 1.4 mm. in height in Lead III.

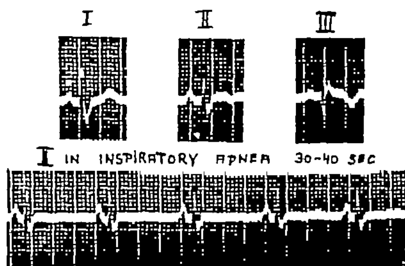


Fig. 3. See text.

parison is then made between the electrocardiogram taken before and that taken during the last seconds of inspiratory apnea. The alterations observed pertain to the T wave and the S-T segment. The T wave decreases progressively in height and becomes isoelectric or negative. The S-T segment dips progressively below the isoelectric line. The chief mechanism of these changes lies in the falling oxygen content of the arterial blood. In cases of diseased coronary arteries this hypoxemia may evoke electrocardiographic alterations in both the ventricular and the atrial musculature. Fig. 3 is the case of a 45-year-old cardiac patient with angina pectoris whose resting electrocardiogram shows right bundle branch block with negative T waves in Leads II and III. The P wave in Lead II is 1.8 mm. in height and 0.08 sec. in duration. In the electrocardiogram inscribed at the end of the inspiratory apnea from 30 to 40 seconds the P wave increases in height to 2.4 mm. and shortens in duration to 0.06 sec. It becomes more peaked not so much because of altered position of the diaphragm—respiratory changes are less marked in Lead II than in Lead III—but because of increasing hypoxemia.

The marked rightward deviation of the electrical axis in P pulmonale of coronary origin is not determined by positional changes. Whereas in cases of true P pulmonale the affected patients usually present a low position of the diaphragm and a centrally located elongated heart shadow in vertical position, coronary patients exhibit a normal or elevated position of the diaphragm and x-ray films reveal a horizontal heart shadow. In this case rightward deviation of the electrical axis of the atria cannot be produced by positional changes in the diaphragm. Disturbances in coronary circulation may affect the musculature of the left atrium, which frequently dilates and may cause rightward shift of the atrial vector because of passive preponderance. In fact, Sano and associates[31] describe a frequent enlargement of the left atrium in the presence of tall peaked P waves in Leads II and III. The position of the atrial vector depends on the synthesis of all vectorial forces developing in the musculature of both atrial cavities. When there is a lesion of the musculature of the left atrium, the vectorial forces produced in that cavity diminish, whereas those in the right atrium predominate and so produce a shift of the atrial vector toward the right.

Summary

Thirty patients with angina pectoris presented P pulmonale waves of coronary origin. The linear and angular structure of these waves was minutely studied and compared with the structure of true P

pulmonale waves. Disturbances in the coronary circulation cause changes not only in the ventricular complex of the electrocardiogram but also in the atrial wave. Tall peaked P waves are the morphologic responses of the atrial musculature to the alterations of hypoxemia. Rightward shift of the electrical axis of the atria is caused by lesion of the left atrial musculature which by passive electrical preponderance expresses the prevalence of the unaltered vectorial forces of the right atrial cavity.

REFERENCES

1. Master, A. M.: P wave changes in acute coronary occlusion, Am. Heart J. 8:462, 1933.
2. Wood, F. C., and Wolferth, C. C.: Huge T waves in precordial leads in cardiac infarction, Am. Heart J. 9:706, 1934.
3. Dressler, W., and Roesler, H.: High T waves in the earliest stage of myocardial infarction, Am. Heart J. 34:627, 1947.
4. Freundlich, J.: The diagnostic significance of tall upright T waves in the chest leads, Am. Heart J. 52:749, 1956.
5. Scherer, J., Kahn, M., Bleifer, S., Donoso, E., and Grishman, A.: The atrial vectorcardiogram in health and disease, Am. Heart J. 60:33, 1960.
6. Chou, T. C., and Helm, R. A.: The pseudo P pulmonale, Circulation 32:96, 1965.
7. Chevalier, H., and Thoon, M.: Le vecteur AP moyen (grandeur et direction) calculé sur 180 coeurs normaux entre 12 et 65 ans, Arch. Mal. Coeur 42:333, 1949.
8. A. Dorren, F., Boyadjan, N., Bastenier, N., Collin, J., and Bierlaire, J.: The diagnostic value of the angle alpha of the electrical axis, Arch. Mal. Coeur 44:407, 1951.
9. Lepeschkin, E.: Modern electrocardiography, Baltimore, 1951, Williams & Wilkins Company.
10. Novelo, S.: The pulmonary P wave. Comparative study of the P wave in chronic mitral and pulmonary disease, Arch. Inst. Cardiol. Mexico 15:179, 1945.
11. Burch, G. E., and DePasquale, N. P.: The electrocardiographic diagnosis of pulmonary heart disease, Am. J. Cardiol. 11:622, 1963.
12. Zuckerman, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale, Am. Heart J. 35:421, 1948.
13. Gross, D.: Contributions to the functional morphology of the P wave, Am. Heart J. 61:436, 1961.
14. Wasserburger, R. H., Ward, A. G., Cullen, R. E., Rasmussen, H. K., and Juhl, J. H.: The T-a wave of the adult electrocardiogram: An expression of pulmonary emphysema, Am. Heart J. 54:875, 1957.
15. Macruz, R., Perloff, J. K., and Case, R. B.: A method for the electrocardiographic recognition of atrial enlargement, Circulation 17:882, 1958.
16. Kahn, M., Scherer, L., Wachtel, F., Grishman, A., and Donoso, E.: An evaluation of the ratio of P wave duration to P-R segment in the diagnosis of atrial enlargement, Am. Heart J. 60:23, 1960.
17. Gross, D.: Über die objektive Bewertung der Macruzschen Methode der elektrokardiographischen Bestimmung der Vorhofvergrösserung, Wien. Ztschr. inn. Med. 46:66, 1965.
18. Pipberger, H. V., and Tanenbaum, H. L.: The P wave, P-R interval and QT ratio of the normal orthogonal electrocardiogram, Circulation 18:1175, 1958.
19. Martins de Oliveira, J., and Zimmerman, H. A.: Auricular overloadings, Am. J. Cardiol. 3:453, 1959.
20. Gross, D.: Breath holding as anoxemia test, Cardiologia 32:302, 1958.
21. Sano, T., Hellerstein, H. K., and Vayda, E.: P vector loop in health and disease as studied by the technique of electrical dissection of the vectorcardiogram (differential vectorcardiography), Am. Heart J. 53:854, 1957.

Severe pulmonary hypertension accompanying patent ductus arteriosus

S. Berlind, M.D.
G. Bojs, M.D.
M. Korsgren, M.D.
E. Varnauskas, M.D.
Göteborg, Sweden

Generally there are no diagnostic problems in cases of uncomplicated patent ductus arteriosus with a typical continuous murmur. Only if significant signs of a left-to-right shunt are lacking on chest roentgenography will catheterization or angiography be necessary to distinguish a patent ductus from a fistula between the coronary and pulmonary arteries. More difficult problems arise in cases of patent ductus arteriosus with *pulmonary hypertension*.

The incidence of pulmonary hypertension is about 14 to 17 per cent in consecutive series of patients[28] and as high as 35 per cent[1] and 62 per cent in other reports. The mortality rate is low in surgically treated cases of uncomplicated patent ductus arteriosus but increases progressively with increasing pulmonary hypertension up to about 50 per cent when shunt reversal is present.[1,9] Thus the general opinion has been that patients with pulmonary hypertension *and a dominant right-to-left shunt should not* be operated upon. There are *however* authors who favor closure of the ductus even when the systemic and pulmonary arterial pressures are equal.[4] In such severe cases the operation is not always followed by a substantial decrease in pulmonary arterial pressure. The conclusion has been that structural changes in the media and the intima of the small pulmonary arteries are responsible for the persistence of pulmonary hypertension.[7,11,13,28] Considering that the number of patients with severe pulmonary hypertension successfully operated on and later reinvestigated hemodynamically is small, we wish to *add our limited experience to the available literature.*

Analysis of cases

Since 1960, 29 patients with the diagnosis of patent ductus arteriosus have been investigated at the clinic. Three patients had been operated upon earlier and were admitted for follow-up investigation. All cases are classified in four groups according to pulmonary arterial pressure (Table I).

Only in the first group were some of the patients subjected to operation without previous catheterization. *All patients in this* group had continuous murmurs. Heart volume was normal or slightly increased except in one patient in whom enlargement of the heart up to 660 ml. per square meter of body surface area was measured.

From the First Medical Service, Sahlgrenska Sjukhuset, University of Göteborg, Göteborg, Sweden.
This study was supported by a grant from the Swedish National Association Against Heart and Chest Diseases.
Received for publication May [illegible], [illegible].

Table I Number of patients with patent ductus arteriosus diagnosed or followed up at the clinic from 1960 through 1965

		Groups according to pulmonary arterial pressure			
		1	2	3	4
		Normal or not measured	30-69 mm. Hg	70-89 mm. Hg	≥90 mm. Hg
29	Patients in total	16	3	3	7
23	Patients submitted to operation	14	3	2	4

Thirteen patients had pulmonary hypertension, i.e. systolic pulmonary arterial pressure higher than 30 mm. Hg (Groups 2-4). Seven patients had systolic pressures exceeding 90 mm. Hg and 5 of them even had equilibrated pressures in the pulmonary artery and aorta.

The clinical and hemodynamic data in 13 patients with pulmonary hypertension are presented in Table II. All of these patients had symptoms of more or less marked dyspnea. Those patients with equilibrated pulmonary arterial and aortic pressures were also cyanotic and polycythemic. All of the patients in Group 2, and 1 patient in Group 3 had continuous murmurs. In the other patients there were various auscultatory findings. Six of them had high-frequency diastolic murmurs suggestive of pulmonary insufficiency. Patients I.L. and D.A. had a Grade 4-5 systolic murmur at the apex and fourth left intercostal space. Ventricular septal defect was suspected. However, that was excluded by catheterization and angiography. Functional mitral regurgitation was confirmed, which is not a rare finding in patent ductus arteriosus complicated by left ventricular failure. A bidirectional shunt was demonstrated in all but 1 patient in Group 4. Patient S.Ö. had only a right-to-left shunt through a wide patent ductus, demonstrated by catheterization. Other patients showed left-to-right shunts. In all patients the catheter was put rather easily through the ductus into the aorta. In 7 patients (C.M., K.E., U.J., D.A., G.J., A.W., H.H.) angiography also was performed. The patent ductus was complicated by additional defects in 2 patients. Patient G.J. demonstrated a small septal defect at the site of the foramen ovale. Patient U.J. had an atrial septal defect and an abnormal pulmonary vein and was lacking the inferior caval vein. Surgical treatment was considered to be contraindicated in this case. The patient was treated with 20 millicuries of [illegible] to lower the metabolic requirements for oxygen.

In an attempt to determine the effect of vasoconstriction on the pulmonary pressure, Patients 1-5 were allowed to breathe pure oxygen for 10 minutes, and then the pulmonary arterial and aortic pressures were measured simultaneously and samples of blood were taken for analysis of oxygen content. The results of this study were not conclusive because of too small changes in pressure and the increase in oxygen saturation in both arterial and venous blood. However, in Patient S.Ö. the pulmonary arterial pressure consistently exceeded the aortic pressure.

In order to study the morphology of the pulmonary vessels, wedge angiography was performed.[4] In Patients R.Q., S.Ö., and U.J., contrast material was injected through a catheter with the tip in the wedge position in the left lung. The x-ray picture obtained showed a narrowed and tortuous arterial tree. The density of the small vessels was reduced. This picture is typical for pulmonary hypertension of any cause. In Patient R.Q. the procedure was repeated about 6 years after operation. The angiogram obtained in the same vessel segment

Table II Patent ductus with pulmonary hypertension (Groups 2-4 from Table I)

Patient	Sex	Age at first examination	Symptoms	M murmur		ECG signs	Hb (Gm./100 ml.)		Heart volume (ml./M² BSA)		Pressure preop		Oxygen content preop			Operation	PA pressure postop
				Preop.	Postop.		Preop.	Postop.	Preop.	Postop.	PA	Ao	RV	PA	A		
Group 4 Systolic PA pressure ≥ 90 mm. Hg																	
1. R.Q.	M	30	Dyspnea palpitations	S + D	0	SR + LVH + RVH	17.0	16.4	470	320	76/40 61	114/51 81	60	75	84	+	6 yrs. postop. 34/10 14
2. G.M.	F	16	Dyspnea	S + D	S	SR + LVH + RVH	15.6	12.8	690	500	145/55 88	147/64 90	59	67	87	+	1½ yr. postop. 55/30 40
3. I.L.	F	37	Heart failure	S	S	AF + LVH + RVH	19.0	14.7	1,140	770	155/76	164/79	30	73	81	+	4 mo. postop. 51/23 40
4. O.	F	18	Dyspnea, cyanosis	S + D	—	SR + RVH	21.6	—	380	—	101/61 75	90/56 4	65	65	84	—	—
5. K.E.	F	1	Dyspnea, cyanosis	S + D	—	SR + RVH	15.5	—	420	—	103/68 85	105/66	72	57	59	—	—
6. I.L.	F	4	Dyspnea	S	S	SR + LVH + RVH	—	12.7	740	540	90/58	120/60	65	57	64	++	12 yr. after first operation 35/23 28

7. U.J.	F	27	Dyspnea, cyanosis, hemoptysis	S	—	SR + RBBB	9.6	—	630	—	$\frac{65}{42}56$	$\frac{97}{64}78$	79	81	81	—	—		
Group 3. Systolic PA pressure 75-90 mm. Hg																			
8. M.L.	F	18	Dyspnea	S + D	S	SR + LVH + RVH	11.5	—	505	450	$\frac{77}{38}50$	—	87	77	96	+	6 yr postop.	$\frac{56}{28}41$	
9. D.A.	F	33	Dyspnea	S + D	S	SR + LVH	13.8	15.0	420	410	$\frac{4}{31}$	$\frac{119}{41}77$	70	87	97	+	—		
10. O.J.	F	23	Dyspnea, palpitations	C	—	SR + RVH	13.4	—	590	—	$\frac{72}{32}47$	—	77	88	95	—	—		
Group 2. Systolic PA pressure 30-60 mm. Hg																			
11. A.W.	F	23	0	C	—	SR + LVH + RVH	12.7	—	570	—	$\frac{83}{28}41$	$\frac{123}{63}$	73	93	—	+	—		
12. H.J.L.	F	63	Dyspnea, edema	C	0	AF + LVH	12.8	12.5	890	770	$\frac{39}{24}28$	$\frac{220}{80}131$	84	78	—	+	—		
13. M.O.	F	34	0	C	—	SR + LVH	13.4	—	520	—	$\frac{30}{19}24$	$\frac{134}{60}104$	71	81	97	+	—		

S, Systolic. *D*, Diastolic. *C*, continuous. *R*, Rhythm. *AF*, Atrial fibrillation. *LVH*, Left ventricular hypertrophy. *RVH*, Right ventricular hypertrophy. *RBBB*, Right bundle branch block. *PA*, Pulmonary artery. *A*, Aorta. *RV*, Right ventricular. *Preop*, Preoperatively. *Postop*, Postoperatively. *0*, None.

was unchanged when compared with pre operative pictures, in spite of normalized pulmonary arterial pressure (Fig 2) In Patient S Ö the x ray picture showed the same hypertensive appearance before and after local infusion of Priscol

Six patients of Groups 3 and 4 underwent operation without any complications. In all cases the ductus was wide and short. In Patients M.A and I E. the ductus was ligated but only partially so in Patient I E. at the time of first operation Fourteen years later when the pulmonary arterial pressure was almost normal complete closure of the ductus was performed In the other 4 patients, division of the ductus was made In Patients R Q and I L the pulmonary arterial pressure did not change after a temporary occlusion of the ductus before the division In Patient M.A a lung biopsy was performed at the time of the operation and the histologic picture was normal Artificial ventilation was given for a few days after operation in Patients 1 3

At follow up investigation all patients were improved A marked decrease in heart volume was demonstrated in the 6 patients of Groups 3 and 4 who were operated upon Five patients were recatheterized The pulmonary arterial pressure had decreased in all cases. In Patient R Q the pulmonary arterial pressure was already normal at 3 months after operation In Fig 1 the relationship between the pulmonary arterial pressure and blood flow is illustrated in 3 patients before and after operation A decrease in pulmonary resistance after operation occurred in Patients R Q and I L. Patient G M showed a lower pulmonary arterial pressure probably due to a decrease in the pulmonary blood flow The accuracy of the calculation of pulmonary blood flow depends on the accuracy in obtaining the representative samples of blood for mixed venous and shunt flow in the pulmonary vascular bed The present calculations were made so that pulmonary blood flow was somewhat overestimated rather than under estimated The preoperative values for pulmonary resistance which can be derived from Fig 1 are probably too low Thus the decrease in resistance postoperatively is not overestimated The pulmonary capillary pressure is disregarded because a normal pulmonary capillary pressure probably had no influence on pulmonary resistance[14] in cases such as these.

The good improvement after the closure of the ductus was especially remarkable in Patient I L. Preoperatively she was in

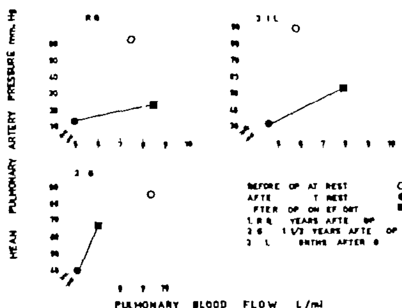


Fig 1 Relationship between pulmonary arterial pressure and blood flow in 3 patients before and after operation.



Fig. Pulmonary edge angiogram recorded in almost the same segment of the lower lobe of the left lung before (A) and 6 years after (B) operation. The angiograms differ from each other with respect to venous filling. The arterial tree shows the same tortuosity of vessels and lack of vascular density on both occasions.

heart failure with a very large heart and atrial fibrillation. About 5 months after operation the heart volume had decreased to 770 ml. per square meter of body surface area. She was defibrillated by D.C. shock and even a cholecystectomy was performed at that time.

Also of interest is the course of disease in Patient U.J. who was not operated upon but who was treated with I[131]. She was still in good condition 6 years after the first catheterization when she already had equilibrated pressures in the pulmonary artery and aorta. The heart volume had increased to 800 ml. per square meter of body surface area but no signs of heart failure were apparent.

Discussion

The decision favoring surgery in patients with equilibrated pressures in the pulmonary artery and aorta (Patients 1, 2, and 3) was made because of the roentgenologic and hemodynamic signs of a left-to-right shunt. The belief was that elimination of the transmission of the aortic pressure wave into the pulmonary vascular bed might decrease the pulmonary arterial pressure even when a right-to-left shunt coexisted. Furthermore, it is difficult to assess which shunt is dominant, especially when one keeps in mind the fact that the experimental procedure may cause the flow through the ductus to fluctuate.

The hemodynamic results presented in Fig. 1 demonstrate that a substantial decrease in pulmonary vascular resistance may occur when the ductus is closed even when shunt reversal is present. In 2 patients (R.Q. and I.L.) the pulmonary arterial pressure was lower after operation even when the pulmonary blood flow was increased by exercise to preoperative levels or higher. This decrease in resistance may have been due to a release of preoperatively existing vasoconstriction or to a reduction in the structural changes in the vessel walls. The rather rapid postoperative decrease in resistance in Patient R.Q. favors the first possibility. Consequently, the degree of preoperative vasoconstriction can apparently reach considerable levels (Patients R.Q. and I.L.). No decrease in pulmonary resistance was found in Patient G.M., which suggests that the postoperative drop in pressure wa

due to decreased pulmonary blood flow only. The age factor may have had some influence in this case.

The mechanism causing the pulmonary resistance to decrease after closure of the ductus is obscure. Reasonably, cessation of the propagation of the aortic pressure wave into the pulmonary vascular bed can be considered to be one of the major factors responsible; the stretch stimulation of the pulmonary vessel wall is then eliminated. This hypothesis is supported by the prevalence of short and wide ductus in patients with severe pulmonary hypertension.[29] The elimination of the left-to-right shunt flow may certainly contribute to a decrease in pulmonary arterial pressure. However, it is not clear to what extent this reduction in flow could contribute to a decrease in resistance. There is no direct correlation between the resistance and the size of the shunt.

Lung biopsy is appreciated by some authors as a means of obtaining information preoperatively in regard to the histopathology of the pulmonary vasculature in cases of pulmonary hypertension. However, it seems that the correlation is poor between the degree of elevation of pressure and the degree of vascular changes. Furthermore, in Patient M.A., normal lung biopsy was obtained in spite of a rather high pulmonary arterial pressure at the time of operation and the pressure was still high 6 years later.

The findings in Patient S.Ö. caused considerable discussion, since the pulmonary arterial pressure exceeded the aortic and there were no signs of a left-to-right shunt. The total heart size was within normal limits. The right ventricle was markedly hypertrophied but there were no signs of left ventricular hypertrophy on either the electrocardiogram or the roentgenogram. This picture apparently corresponds with that of primary pulmonary hypertension. It is thus suggestive that the equilibration of pulmonary arterial pressure with aortic pressure was due to prenatally developed and later on retained high pulmonary vascular resistance in this case. Pulmonary hypertension found in other patients with concomitant enlargement of the heart, including enlargement of the left ventricle, was probably secondary to the left-to-right shunt. From the beginning, a predominant left-to-right shunt may lead to overloading and dilatation of the left ventricle. The increased flow, together with the transmitted aortic pressure, may cause progressive functional and structural changes in the pulmonary vascular bed.[1] This reasoning favors the classification of the pulmonary hypertension that accompanies patent ductus arteriosus into primary and secondary types. No reduction in the pulmonary arterial pressure is to be expected after closure of the ductus in the primary type.[1, 41]

No definite conclusion can be drawn with regard to the prognosis in this patient. However, the survival time in Patient U.J. suggests that the prognosis is probably better in patients in whom pulmonary hypertension accompanies the patent ductus arteriosus than in patients with essential pulmonary hypertension. Similar survival times have been noted also by other investigators. The beneficial results of the Blalock operation in the treatment of primary pulmonary hypertension[7] would further suggest that the patent ductus accompanied by the primary type of pulmonary hypertension should not be occluded.

Summary

The patent ductus arteriosus was closed in 3 patients who had equilibrated pressures in the pulmonary artery and aorta with excellent clinical and hemodynamic results. The presence of a right-to-left shunt does not contraindicate operation if there is also a left-to-right shunt. A marked decrease in pulmonary vascular resistance may occur postoperatively in spite of a lack of change in the pathology of the pulmonary arterial tree angiographically.

The concomitant existence of enlargement of the left ventricle and consequently enlargement of the total heart size suggests that the pulmonary hypertension is of secondary type and thus may be influenced beneficially by the operation.

With no signs of a left-to-right shunt and with the cardiac size within normal limits, the picture resembles that of primary pulmonary hypertension. Surgical treatment could be expected to have a beneficial effect if vasoconstriction of considerable degree could be demonstrated to exist in this type of patient. This question requires further study.

Professor G. Biorck has kindly permitted us to publish the hemodynamic findings of the preoperative study in Patient No. 8 (M.A.). The surgical treatment of the 21 patients was performed by V. P. Berg and E. Linder of Goteborg, S. Ekestrom, of Stockholm, and H. Wulff of Malmö.

REFERENCES

1. Anabtawi, I. N., Ellison, R. G., and Ellison, L. T. Natural history of pulmonary hypertension in surgically treated patent ductus arteriosus, Suppl. I Circulation 31:61, 1965.
2. Antonius, N. A., Mazzar Iti, L. G., and Creech, A. D. Surgical closure of atypical patent ductus arteriosus, J. Thoracic Surg. 31:332, 1956.
3. Berå, L., Tamlin, S., and Varnauskas, E. Pulmonary wedge angiography. Experimental investigation in dogs, Acta Radiol. 57:209, 1962.
4. Biorck, G., and Wulff, H. B. Öppenstående ductus arteriosus hos vuxna, Svensk läk. tidn. 53:198, 1956.
5. Campbell, M. Patent ductus arteriosus: some notes on prognosis and on pulmonary hypertension, Brit. Heart J. 17:511, 1955.
6. Cleland, W. P. Symposium on congenital heart disease. (3) The level of pulmonary vascular resistance that contraindicates operation, Brit. Heart J. 20:276, 1958.
7. Edwards, J. E., Douglas, J. M., Burchell, H. B., and Christensen, N. A. Pathology of intrapulmonary arteries and arterioles in coarctation of aorta associated with patent ductus arteriosus, Am. Heart J. 38:205, 1949.
8. Ellasch, H., Eriksson, K., and Werko, L. Patent ductus arteriosus in the adult, Acta Med. Scandinav. 155:135, 1956.
9. Ellis, F. H., Kirklin, J. W., Callahan, J. A., and Wood, E. H. Patent ductus arteriosus with pulmonary hypertension. An analysis of cases treated surgically, J. Thoracic Surg. 31:268, 1956.
10. Gammelgaard, A., Solem, G., Therkelsen, F., and Boesen, I. Late results of operation for patent ductus arteriosus in infants, especially those with pulmonary hypertension, J. Cardiovas. Surg. 6:34, 1965.
11. Harris, P. Patent ductus arteriosus with pulmonary hypertension, Brit. Heart J. 17:85, 1955.
12. Harris, P., and Heath, D. The human pulmonary circulation, Edinburgh and London, 1962, E. & S. Livingstone, Ltd., p. 157.
13. Kjellberg, S. R., Mannheimer, E., Rudhe, A., and Jonsson, B. Diagnosis of congenital heart disease, ed. 2, Chicago, 1959, Year Book Publishers, Inc., p. 546.
14. Paulin, S., and Varnauskas, E. PCV-angiografi, (Sv. fören. med. radiologi), Nord. Med. 67:70, 1962.
15. Permutt, S., and Riley, R. L. Hemodynamics of collapsible vessels with tone: The vascular waterfall, J. Appl. Physiol. 18:924, 1963.
16. Reid, J. M., Stevenson, J. G., Coleman, E. N., Barclay, R. S., Welsh, T. M., Fyfe, W. M., and Inall, J. A. Moderate to severe pulmonary hypertension accompanying patent ductus arteriosus, Brit. Heart J. 26:600, 1964.
17. Storstein, O., Efskind, L., Muller, C., Rokseth, R., and Sander, S. Primary pulmonary hypertension, with emphasis on its etiology and treatment, Acta Med. Scandinav. 179:197, 1966.
18. Taussig, H. B. Congenital malformations of the heart, Vol. 2, Specific malformations, ed. 2, Cambridge, Mass., 1960, Harvard University Press (published for the Commonwealth Fund), pp. 448 and 490.
19. Varnauskas, E., Narta, E., and P[illegible]lin, S. Coronary arteriovenous fistula simulating patent ductus arteriosus. To be published.
20. Wood, P. Pulmonary hypertension, with special reference to the vasoconstrictive factor, Brit. Heart J. 20:557, 1958.

Variables affecting the splitting of the second heart sound in atrial septal defect

*Robert F Castle M.D.**
Chapel Hill N C

Of the common congenital cardiac lesions, isolated ostium secundum atrial septal defects are probably the most difficult to recognize clinically with reasonable certainty in early childhood Often the systolic pulmonary ejection murmur which accompanies this condition is rather unimpressive, and there may be a tendency to dismiss it as an innocent murmur In the evaluation of such murmurs much emphasis has been placed on the importance of careful analysis of the nature of splitting of the second heart sound as a valuable aid in allowing differentiation of innocent pulmonary ejection murmurs from those associated with atrial septal defects.[1-6]

In spite of the well-established relationship between the presence of an atrial septal defect and wide "fixed" splitting of the second heart sound several authors have noted that exceptions do occur [7] Moreover as children with documented atrial septal defects were followed for prolonged periods, it appeared that some of the younger children exhibited respiratory variation in the splitting of the second sound that was not distinguishable from normal and that the splitting in some of these patients increased with age A representative phonocardiogram from one such child is shown in Fig 1

The present study was designed to study the effect of age upon splitting of the second heart sound in uncomplicated secundum atrial septal defects. The relationship of the heart rate and the size of the shunt to the pattern of splitting was also evaluated

Methods

Forty-one patients with ostium secundum atrial septal defects were included in this series. These patients ranged in age between 18 months and 25 years. No patient exhibited or had a history of congestive failure All patients underwent right heart catheterization and data were collected which permitted the calculation of pulmonary-to-systemic flow ratios (the Qp/Qs ratio) These ratios ranged between 1 5 and 7 6. No patient had elevated pulmonary vascular resistance.

Phonocardiograms were recorded with the Sanborn Twin Beam apparatus, using the standard dynamic microphone with a diaphragm chest piece The tracings obtained over the second left intercostal space were analyzed A paper speed of 75 mm per second was employed This permitted measurement of individual time intervals to the nearest 0 005 second (.375 mm) Splitting intervals were measured

Supported by North Carolina Heart Association Grant 324 Hen 16 and North Carolina Medical School Grant 324 UNI 1 156.

Received for publication May 26 1964

*Formerly Assistant Professor of Pediatrics, University of North Carolina School of Medicine Chapel Hill, N. C. At present Associate Professor of Pediatrics, Department of Pediatrics, University of New Mexico School of Med- ine Albuquerque N. Mex., 7110

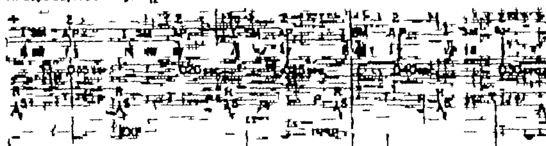




Fig. 1. Serial phonocardiograms in young child with proved ostium secundum atrial septal defect, showing increased splitting of the second sound with age. *A*, This tracing, obtained when the child was 2 11/12 years old, shows variable splitting of the second sound ranging between 0.020 and 0.040 second. The pattern and magnitude of respiratory movement of the two components of the second sound are normal. *B*, When the child was 5-8/12 years old, the splitting had widened, although some variability in the interval between the aortic and pulmonic components of the second sound persisted. Heart rates are equivalent in the two tracings.

during three respiratory cycles in each patient. The range of splitting of the two components of the second sound was determined, as was the mean splitting of the second sound. Heart rate was calculated from the simultaneous electrocardiogram.

The influence of the pulmonary-to-systemic flow ratio (Qp/Qs ratio), heart rate, and age on mean splitting of the second heart sound was analyzed by the method of multiple linear regression employing the UNIVAC 1105 computer. Minimal and maximal splitting were also related to Qp/Qs ratio, heart rate, and age.

A variance analysis was performed for each age in order to determine whether the range or variability of respiratory splitting changed with age.

Results

No significant correlation exists between the indexed size of the defect and mean, minimum, and maximum splitting of the second sound (Fig. 2,*A-C*).

A significant inverse correlation exists between heart rate and mean splitting of the second sound ($r = -0.49$, significant at $\alpha = 0.05$) (Fig. 3,*A*). A similar negative correlation exists between heart rate and minimum and maximum splitting (Fig. 3,*B* and *C*).

Age is positively correlated with mean splitting of the second sound ($r = +0.59$, significant at $\alpha = 0.01$) (Fig. 4,*A*). A parallel positive correlation exists between age and minimum and maximum splitting (Fig. 4,*B* and *C*).

The variability or range of respiratory splitting of the second sound was unrelated to age in this series. Thus, although average splitting was less in the younger age groups, inspiratory and expiratory variation in splitting from the mean was similar in all ages. Ten of our 41 patients exhibited a variability in splitting of 0.015 second or greater.

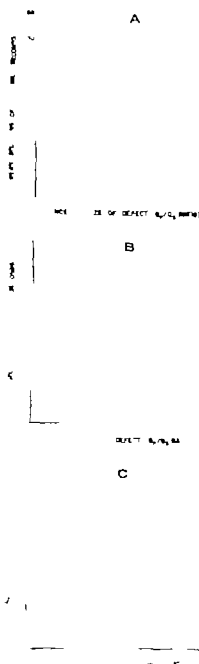


Fig. 2. Relationship of indexed size of the defect (Qp/Qs ratio) t patterns of splitting. A demonstrates the lack of significant relationship between mean splitting of the second sound and the Qp/Qs r tio (= 11). A similar nonsignifica t relationship is noted bet een indexed ize of the defect and minimum (B) and maximum (C) splitting.

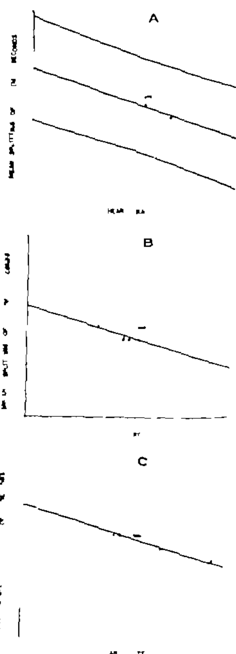


Fig. 3. Relationship of heart rat t pattern of splitting. A demonstrates the in erse relationship of heart rat to mean splitting of the second sound ($r = -0.49$ significant t = 0.05). The upper and lower lines enclose the 95 per cent prediction range for the splitting alues. B nd C how simila relationship of heart rat t minimum and ma m m splitt ng. The lope of the regression line is nea ly identical f ll three graphs.

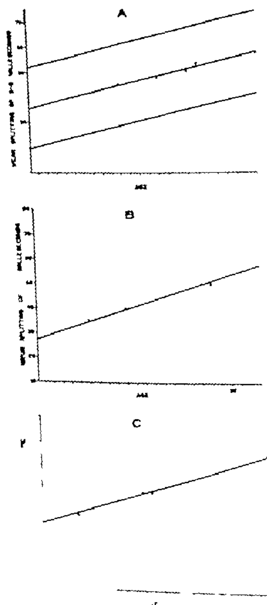


Fig. 4. Relationship of age to pattern of splitting. A demonstrates the direct relationship of age to mean splitting of the second sound (r = +0.59, significant at the 0.01). The upper and lower lines enclose the 95 per cent prediction range for the splitting values. B shows a similar direct relationship of minimum splitting to age. Note that, with one exception, the patients exhibiting minimal splitting of 0.03 second or less were 12 years of age and under. C shows the direct relationship of age to maximum splitting. Note that patients exhibiting maximum splitting greater than 0.03 second are in the older age group.

Discussion

This study has confirmed the clinical impression that splitting of the second heart sound in children with uncomplicated atrial septal defects generally becomes wider with age. Moreover, the effects of age are not explained solely on the basis of a trend toward slower heart rates in the older subjects, since an independent correlation exists between the described patterns of splitting and both age and heart rate. Although it is generally believed that the largest shunts are associated with the widest splitting, no relationship was found between the indexed size of the shunt and the width and degree of variation in splitting of the second sound. However, it should be noted that no patients with very small shunts (i.e., with Qp/Qs ratios less than 1.5) are included. In this group, the width and variability of splitting may be normal or nearly normal throughout life.

The failure to find a significant relationship between the indexed size of the shunt and the degree of splitting of the second sound was somewhat surprising. One might speculate that the ability of the right ventricle to prolong its duration of systole in response to a volume load is rather narrowly limited. In the presence of an atrial septal defect, an increased rate of right ventricular ejection is obviously a much more important mechanism of adaptation to volume loading than is an increased duration of right ventricular systole.

The inverse relationship of heart rate to splitting of the second sound is not unexpected. At faster rates, there is a smaller discrepancy between the stroke volumes of the two ventricles, the length of systole of each ventricle is shorter, and differences in the duration of systole between the two ventricles are smaller. These differences primarily involve mean splitting, for the respiratory variation or range of splitting is not significantly affected by the presence of moderate tachycardia.

The direct and independent correlation of age with the degree of splitting of the second sound is probably the most significant finding in this study. The physiologic bases for this relationship are uncertain at this time. One factor probably relates to the slow maturation in structure

and function from the high-pressure low compliance right ventricle of the fetus to the distensible adult type of right ventricle Prolongation of right ventricular systole in response to a volume load may become more apparent as the high-compliance volume pump characteristics of the right ventricle become fully developed over the early years of life.

In the normal infant there is a rapid transformation of the thick walled muscular pulmonary arteries of the neonate to the thin walled low resistance vessels of the child and adult. This ordinarily occurs by 3 months of age By this time, the adult disproportion in thickness between the two ventricles also has become evident [16] In spite of these anatomic changes, the electrocardiogram shows a much slower resolution of the early right ventricular dominance In the infant with an atrial septal defect, the rate of fall in the pulmonary vascular resistance may be slower than in the normal infant. Although there is no direct proof of this point as yet, such a mechanism would help explain the ordinarily slow evolution of the pattern of splitting in the presence of an atrial defect since a mild increase in right ventricular outflow resistance has been demonstrated to result in shortening of right ventricular systole [1]

Wide splitting of the second sound does develop at different rates in different infants and children Occasionally in infants the transition to clearly abnormal splitting may occur in a matter of months rather than over the usual period of several years. In two published reports of series of infants with atrial septal defects who had very large shunts and exhibited congestive failure wide splitting of the second sound was described as a consistent physical finding [12,13] However in other series of infants in which congestive failure was not present [11-13] normal patterns of splitting were described These observations also are compatible with the theory that wide splitting of the second sound in atrial septal defect is related to the development of a high-compliance right ventricle and low resistance pulmonary vascular bed Those small infants exhibiting very large shunts and congestive failure may represent a group in which such a state is achieved through an unusually rapid and complete involution of the fetal pulmonary circulatory pattern In this group the left-to-right shunt may rapidly increase in magnitude whereas in the usual infant with an atrial septal defect a gradual increase in the size of the shunt is thought to occur [4]

Another factor which may be involved in the slow acquisition of wide splitting of the second sound in atrial septal defect is the development of a contractile form of infundibular pulmonary stenosis. If this state exists, there may be delayed protodiastolic relaxation of the region of the outflow tract of the right ventricle and an associated delay in closure of the pulmonary valve. This process was described by Johnson[17] in a variety of lesions including atrial septal defect. In milder forms it need not be associated with a significant pressure gradient across the *pulmonary outflow tract We have not* been able to demonstrate this process consistently in children but it may contribute to the effects of age in some patients

Although the electrocardiographic finding of so-called incomplete right bundle branch block evolves in most patients with atrial septal defects, this probably represents the effect of the development of a large volume right ventricle perhaps associated with *hypertrophy of the region of the outflow tract [18] However this cannot* be considered to be a cause for the wide splitting since there is no delay in the initiation of right ventricular contraction [18] Moreover in the postoperative period after successful repair of an atrial septal defect the pattern of splitting usually returns to normal before significant changes appear in the electrocardiogram Complete right bundle branch block is rarely noted in patients with atrial septal defects. Here, a true conduction disturbance exists, the onset of right ventricular systole is delayed and exceptionally wide splitting occurs as the combined effect of bundle branch block and the presence of an atrial septal defect.

The effects of age upon splitting of the second sound have their greatest clinical implication with respect to the problem of evaluating pulmonary ejection *murmurs*

in infants and young children In the young child with an atrial septal defect, the average splitting of the second sound is often relatively narrow (in the range of 0 030 second) If in addition a child in this group demonstrates respiratory variation in splitting of 0.015 second or greater he falls within the normal population with respect to this parameter

This series of patients did not demonstrate a consistent change in the range or variability of splitting with age from 18 months to 25 years. However other series which include infants in the first year with atrial septal defects indicate that normal variable splitting is very common at that age. [15] Thus, auscultatory errors in the diagnosis of this condition are most apt to occur in infants.

Boyer and Chisholm and Shafter[20] have suggested that helpful diagnostic information can be obtained by studying respiratory movement of the aortic component of the second sound in patients with suspected atrial septal defects. In normal subjects, expiratory decrease in splitting is due to later closure of the aortic valve, as well as to an earlier occurrence of the pulmonary component of the second sound.[20, 22] In the patient with an atrial septal defect, as in the normal individual expiration is associated with a decrease in the systemic venous return However with an atrial septal defect there is a reciprocal expiratory increase in the left to-right shunt. This is associated with a decrease in left ventricular filling and a concomitant expiratory shortening of left ventricular systole Thus, in the presence of an atrial septal defect, the two components of the second sound often move in a parallel fashion with respiration. This is thought to be a major factor contributing to the relative constancy of the splitting interval

We have not found the sign of reversed respiratory movement of the aortic component of the second sound to be a common finding in young children with atrial septal defects. In many cases, no movement could be measured and often the normal pattern of a slight expiratory delay in the timing of the aortic component of the second sound has been observed Similar findings were noted by Shafter [20] whose data demonstrate in his adult patients a greater and more consistent reversed movement of the aortic component of the second sound with respiration.

Summary

This phonocardiographic study of 41 children and young adults with uncomplicated ostium secundum atrial septal defect has resulted in these findings (1) No correlation could be found between mean splitting and the pulmonary to-systemic flow ratio. (2) A positive correlation ($r = 0.59$ significant at $\alpha = 0.01$) was observed between age and mean splitting (3) An inverse correlation was noted between heart rate and splitting ($r = -0.49$ significant at $\alpha = 0.05$) Possible mechanisms responsible for these relationships are discussed

A major clinical implication of these findings relates to the evaluation of pulmonary ejection murmurs in infants and young children In these age groups, an atrial septal defect may exist in the presence of a normal or nearly normal pattern of splitting of the second heart sound

REFERENCES

1 Barber J M., Magidson, O and Wood, P Atrial septal defect, with special reference t electrocardiogram, pulmonary artery pressure and second heart sound, Brit. Heart J 12:277 1950.
2. Leatham, A., and Gray L Auscultatory and phonocardiographic signs of atrial septal defect, Brit. Heart J 18 193, 1956.
3. Perloff J K., and Harvey W P Mechanisms of fixed splitting of the second heart sound, Circulation 18:998, 1958.
4. Aygen, M. M and Braunwald, E The splitting of the second heart sound in normal subjects nd in patients with congenital heart disease Circulation 25:328, 1962.
5. Schrire, V and Vogelpoel, L. Atrial septal defects, Am. Heart J 68:263, 1964.
6. Braunwald, E., Aygen, M M., and Ross, J., J Auscultatory nd phonocardiographic findings in atrial septal defects, in Segal, B L., editor The theory and practice of uscultation, Philadelphia, 1964 F A. Davis Co., p. 193
7 Dimond, E. G., and Benchimol, A.: Phonocardiography in trial septal defect Correlation between hemodynamics and phonocardiographic findings, Am. Heart J 58:343, 1959
8. Eisenberg, R., and Haltgren, H. N Phonocardiographic features of atrial septal defect, Circulation 20:490, 1959
9 Evans, J R., Rowe, R. D nd Keith J D

The [illegible] defect [illegible] Am J Med 30 [illegible]

[illegible] J [illegible]

[illegible] J [illegible] J 68 [illegible]

[illegible] J [illegible] J 61 [illegible]

[illegible] Am [illegible] 13 [illegible]

[illegible] 89 [illegible]

[illegible] Cir [illegible] 32 [illegible]

[illegible] A B [illegible] defect [illegible] J [illegible]

[illegible] differentiation from [illegible] Pep 108 [illegible]

[illegible] 1 19

19 [illegible] heart [illegible] defect [illegible] Cir [illegible] 19

[illegible] Am J Card [illegible]

[illegible] 19

[illegible] The [illegible] heart [illegible] Circ [illegible]

Repeated venous and arterial catheterization in man

An analysis of complications

Hugh S Levin M.D
Joseph V Messer M.D
*Joseph Pines M.D***
Wright Patterson AFB Ohio

In the field of biomedical research inherent variability among human subjects complicates evaluation of experimental results. Because of this variability it is sometimes more desirable from a statistical point of view to compare the responses of a single group of individuals to various experimental situations than to compare the responses of different groups, each to a separate condition. This practice in the study of cardiovascular physiology may necessitate several arterial and venous catheterizations, the injection of large amounts of indicator dye and the removal of sizable quantities of blood over the course of a protracted multiphasic experiment. Although the dangers of intravenous and intra-arterial cannulation are well known [3] the hazards of repeated intubation are less clearly defined. Similarly although indocyanine green has proved to be innocuous when used in recommended doses,[4-6] no information is available on how frequently these doses may be repeated and whether allergic or accumulative effects may result from recurrent use of the dye. The present study was undertaken in an attempt to answer these questions.

Materials and methods

Seventeen healthy male Air Force volunteers 18 to 31 years of age underwent one to seven arterial and venous catheterizations over a 7 month period for the purpose of another experiment,[7,8] during the period starting in September 1962 and ending in April 1963. On each occasion after sterile skin preparation and local infiltration with lidocaine hydrochloride, polyethylene catheters (PE 160) sterilized with benzalkonium chloride and thoroughly rinsed with saline were inserted percutaneously according to the technique of Seldinger[9] into a brachial artery and into the central venous circulation through a vein in the same arm. The catheters remained in place for 4 to 6 hours while the

From Aerospace Medical Research Laboratories, Aerospace Medical Division, Air Force Systems Command, United States Air Force, Wright-Patterson AFB, Ohio.
Supported by Air Force Contract No. AF 33(615)-1500 with Tufts University School of Medicine Boston Mass.
Presented in part at the 13th Annual Scientific Session of the American College of Cardiology New Orleans, La Feb 13, 1964.
The voluntary informed consent of the subjects used in this research was obtained as required by AFR 80-8
Received for publication June 2, 1964.
*Present address Creighton University School of Medicine, Omaha, Neb.
**Present address Tufts University School of Medicine, Circulation Laboratory Boston City Hospital, 818 Harrison Ave., Boston, Mass 02118, United States Public Health Service Research Career Development awardee (I-K3-HE-8759)
***Present address Beth Israel Hospital, Boston, Mass.

Table I. Exposures and white blood count

Subject	Age (yr)	Total pa...	1st Interval (days)	2nd Interval (days)	3rd Interval (days)	4th Interval (days)	5th Interval (days)	6th Interval (days)
Group I								
W.N.	23	6	49	33	8	1	39	
R.C.	30	7	46	31	70		15	14
F.W.	8	7		19	83	11	13	12
J.I.	31		28	39	87	1	14	14
R.K.	21	[illegible]	31	33	6	15	13	
D.D.	24	6	36	3	72	2	19	
R.I.	5	6	19	30	5	22	19	
D.I.	25	3				14	14	
R.W.	25	3				14	17	
Group II								
C.B	25	‡	31					
D.Z	30	3	29	35				
H.H	20	3	29	33				
R.B	18	3	25	30				
L.S.§	25	3	29	42				
Group III								
G.G	23	‡						
K.H	26	‡						
R.S.	25	‡						

*Abnormal values are underlined.
†Control values were reported as normal (5,000-10,000 mm³) for some subjects because values were unavailable.
‡Incomplete study.
§Lost to follow-up.

Total dye (mg)	*Total dye (mg/Kg)*	*Total blood loss ( )*	*Time of WBC study*	*Total WBC (5,000-10,000/mm³)*	*Neutrophil (3,000-7,000/mm³ 50%)*
			Control	8 300	5 229 (62%)
			3 day	4 737	2 890 (61)
915	11 4	1 640	60 day	4 423	2 035 (46)
			9 mo.	5 000	2 450 (49%)
			Control	8 950	5 280 (59%)
1,060	17 4	1 972	1 da	6 518	2 738 (42%)
			60 day	6 41	3 270 (51)
			Control	9 200	6 348 (69)
			1 da	4 149	2 199 (53)
931	9 2	1 493	77 day	5 45.	3 653 (67%)
			10 mo	7 700	4 620 (60%)
			Control	8 300	4 648 (56)
1,060	18 3	1 858	1 day	6 881	3 373 (53)
			32 day	5 999	3 240 (54)
			Control	8 100	5 184 (64)
915	12 5	1 507	2 day	5 139	2 724 (53)
			79 day	6 804	3 946 (58 %)
			Control	8 300	5 863 (61)
			1 da	3 171	1 300 (41)
915	13 0	1 511	60 da	3 928	1 414 (36%)
			9 mo.	8 300	4 316 (52)
			Control	9 100	5 733 (63)
971	14 1	1 393	1 day	7 880	5 043 (64)
			66 days	6 512	3 516 (54)
			Control	—	— —
465	5 5	880	3 day	5 23	3 091 (59%)
			60 day	5 086	3 052 (60)
			Control	6 200	3 658 (62)
465	6 0	900	1 day	5 039	3 326 (66)
			6 day	4 309	2 844 (66)
			9 mo.	8 000	— —
160	3 4	73	Control	Normal†	—
			7 mo.	7 851	4 945 (61)
450	6 9	329	Control	Normal†	—
			6 mo.	8 886	5 43 (59%)
450	6 2	323	Control	Normal†	
			6 mo	3 746	1 3 (58)
			12 mo.	400	4 29 (58)
352	4 9	303	Control	Normal†	—
430	8 5	334	3 mo.	5 620	3 83 (68)

subjects underwent exposure to a variety of thermal stresses ranging from 40°F to 160°F. The venous catheter was filled with indocyanine green dye and injections were *made every 7.5 to 15 minutes.* After arterial sampling, the arterial catheter was flushed with heparinized saline at the same interval. Over the 7 month period the subject received up to 1,060 mg. of *indocyanine green* and lost a maximum of 1.9 c.c. of blood, the maximum loss for a single experiment being 33 c.c. (Table I). At the end of each experiment the catheters were removed aseptically and hemostasis was insured by manual compression followed by the application of a nonocclusive pressure dressing which remained in place until the following morning. The interval between exposures for any one subject varied from 11 to 8 days (Table I). Attempts were made to avoid catheterization of the same vein twice consecutively.

Evaluation of complications. Complications were evaluated from three viewpoints: (1) immediate untoward reactions, (2) the status of the veins and arteries several *months after the experiment, and (3) laboratory* evaluation of hematopoietic, renal, and hepatic function after the experiment. All subjects are included in the analysis of immediate complications. For the purpose of evaluating the *clinical* status of the vessels several months after the experiment, subjects were examined by a cardiovascular surgeon unassociated with the project and by one of us (H.S.L.). An estimation of the integrity of the arteries was made by palpation of the brachial, radial, and ulnar pulses, by evaluation of the color, temperature, and capillary filling time of the extremity, and by careful questioning concerning claudication or other symptoms. The veins were examined for nodularity and induration. Distention *with tourniquet occlusion of the upper arm* and rate of emptying with elevation of the extremity were noted.

Laboratory evaluation of hematopoietic, renal, and hepatic function was accomplished by the following tests: white blood count and differential, red cell count, hemoglobin and microhematocrit, platelet count, urinalysis, *blood urea nitrogen,* serum creatinine and uric acid, Van den Bergh, total serum protein, albumin/globulin ratio, cephalin flocculation, thymol turbidity, total serum cholesterol, cholesterol esters, alkaline phosphatase, and *serum oxalacetic transaminase. These tests* were performed by the base hospital, whereas the control blood counts and urinalyses were accomplished by a subsidiary base dispensary before the volun*teers were accepted as subjects for the* original study.

For the purpose of analysis the subjects were divided into three groups (Table I). Group I consisted of 9 subjects with multiple (three to seven) exposures for whom laboratory studies were available shortly after their last catheterization and again 1 to 3 months later. The status of the arm vessel was evaluated approximately 7 months after the last catheterization. Group II consisted of 4 subjects with two or three exposures who had a single vascular and laboratory evaluation 5 to 7 months after their last catheterization. An additional subject in this group (L.S.) was available only for analysis of immediate complications. Group III consisted of 3 *subjects who underwent single arterial* and venous catheterizations but received either an insignificant amount of indocyanine green or none at all because of early termination of the study. The vessels of *these subjects were examined* 8 months after the catheterization. No laboratory evaluation was undertaken.

Results

1. Immediate untoward reactions (*Table II*).

VASOVAGAL REACTIONS. Five subjects developed *vasovagal reactions* characterized by lightheadedness, nausea, sweating, and bradycardia during the first insertion of the arterial catheter. The majority of reactions were mild, transient, and limited to the *initial arterial* puncture. One subject had a similar but milder episode during his second study. One subject, however, developed severe *bradycardia* with a nodal rhythm in addition to the other symptoms described above. This condition persisted for 10 to 15 minutes despite aggressive therapy but rapidly *abated after removal of the arterial needle.* Because of the severity and duration of

Table II *Incidence of immediate complications as related to number of exposures*

Reaction	Exposure number							Complications	
	1	2	3	4	5	6	7	Number	Per cent
Vasovagal reaction	5	1	0	0	0	0	0	6	9
Venospasm and thrombophlebitis	2*	0	0	0	0	0	0	2	3
Severe arterial spasm	1	1	0	0	0	0	0	2	3
Arterial embolization	0	0	0	1	1	2	0	4	6
							Total	14	21

*One subject in each category discontinued from study because of this complication.

the reaction the volunteer was not subjected to further catheterization.

VENOUS SPASM AND THROMBOPHLEBITIS Two subjects complained of significant arm pain during the experiment requiring its termination in one case. In both the cephalic vein had been catheterized in the absence of a satisfactory basilic tributary After removal of the catheters both subjects continued to experience discomfort, and within 24 hours both had evidence of thrombophlebitis of the cannulated vein. In one subject the signs were limited to tenderness, induration and redness of a short segment of vein extending from the site of puncture to about 3 cm above it. The symptoms resolved within 2 to 3 days. The other subject had involvement along the entire course of the vein. Recovery was prolonged (2 weeks) and because of the severity of the symptoms the subject chose to eliminate himself from the study In neither case was there evidence of thrombosis of deep veins or pulmonary embolization.

ARTERIAL SPASM AND OCCLUSION In all but one subject the brachial and radial pulses were palpable although frequently diminished after removal of the catheters. In that subject however the pulses were imperceptible during the entire course of his initial exposure and remained absent for several weeks thereafter during which time he complained of easy fatigability of the arm. A second exposure with the catheters in the opposite arm was terminated because of severe arterial spasm The subject did not undergo further catheterization.

ARTERIAL EMBOLIZATION There was evidence of arterial embolism after 4 of 68 arterial catheterizations (6 per cent) One subject noted the sudden onset of coldness of the index finger approximately 36 hours after the right brachial artery had been catheterized for the third time There was no pain or limitation of motion In addition to the diminished temperature, examination revealed pallor and absent digital pulses in that finger with delay in capillary filling time. The signs diminished over the next week and examination 2 months later revealed questionable residual coldness, minimal delay in filling time, and strongly pulsating digital arteries.

Multiple splinter hemorrhages under several fingernails were noted by one subject 48 hours after his fourth and fifth experiments and by a second subject 72 hours after his sixth catheterization The lesions which were painless, were confined to the arm most recently catheterized and disappeared within 4 to 7 days. There were no systemic signs such as fever murmur or splenomegaly

It seems to be likely that, in these 4 instances, peripheral embolization of thrombotic material arising at or above the site of arterial puncture was responsible for the findings. The fact that at least 36 hours elapsed between the experiment and the onset of the symptoms makes unlikely the possibility that clotted blood or air bubbles infused during the procedure were involved

NEURITIS By far the most common complaint after catheterization was hyperesthesia of the finger tips. This was mani-

fested by tenderness of the finger pads when pressed together or when contact was made with an external object. This symptom was invariably limited to the first three digits and lasted as long as a week. Less commonly, numbness over this area was reported. We think that irritation of the median nerve from direct trauma, local anesthetic solution, or extravasated blood is the most likely explanation for this phenomenon.

INFECTION. Systemic symptoms such as fever, malaise, or fatigue after the experiment were absent in every case. No subject showed evidence of local or systemic infection.

ALLERGIC REACTIONS. At no time was there evidence of immediate or delayed clinical allergic reaction to the intravenous injection of indocyanine green.

BLEEDING. No major bleeding at the site of venous or arterial puncture occurred in the postexperimental period.

Status of arteries and veins several months after the experiment. Sixteen subjects were available for clinical evaluation of catheterized arteries and veins 2 to 8 months after the last catheterization. The subject who had sustained an embolus to his forefinger continued to show questionable coolness of the finger and slight delay in filling time 2 months after the embolization, although the digital pulses in the affected finger were normal. No other subject, including the 2 who had developed splinter hemorrhages and the one who had experienced severe arterial spasm, showed a perceptible arterial abnormality.

Four subjects, including one of the 2 who had experienced acute thrombophlebitis, showed evidence of venous disease as manifested by nodularity, lack of filling with tourniquet occlusion, lack of emptying after elevation of the arm, or complete atrophy of the vein. No symptoms resulted from these isolated venous occlusions. The veins of the second subject who had experienced thrombophlebitis were free of demonstrable disease 1 month later.

3. Laboratory evaluation of hematopoietic, renal, and hepatic function.

WHITE BLOOD COUNTS (Table I).* Subjects in Group I showed a tendency toward leukopenia immediately after their last catheterization. All counts were below pre-experiment levels, the highest being 7,850 cells per cubic millimeter. Three subjects had counts below 5,000 due to absolute neutropenia (1,300 to 2,890), whereas 2 subjects manifested a reduced neutrophil count in the face of a normal total count. One (L.W.) of the 3 subjects had 9 per cent atypical lymphocytes. One subject (R.C.) with a normal total white cell count had eosinophilia (9 per cent) as well as absolute neutropenia.

On re-examination 1 to 3 months later the neutrophil count of 3 subjects, including the one with atypical lymphocytes, had returned to normal. Two subjects continued to show neutropenia, one of these (W.N.) developed atypical lymphocytes (8 per cent) which were not previously reported. An additional subject whose previous count was normal manifested neutropenia. Eosinophilia persisted in one subject (R.C.) and disappeared in the other.

One subject in Group II manifested neutropenia 6 months after his last exposure. A second subject (D.Z.) had mild eosinophilia.

Five of the 7 subjects who had manifested neutropenia at one time or another were re-examined 6 months after their last count. All were found to have normal total white counts, but one subject of Group I continued to show a reduced absolute number of neutrophils.

RED CELL ELEMENTS. With one exception (L.W.), all subjects in Group I showed a drop in hemoglobin the day after their last procedure, averaging 1.4 Gm. per cent (range −0.1 to 2.5 Gm. per cent). The hematocrit fell in half of the subjects, averaging 1 per cent (range −3 to +5 per cent). By the time of the second determination 1 to 3 months later, all but one of the previously depressed hemoglobin levels had risen, but only three equaled or exceeded control levels, the average depression equaled 0.4 Gm. per cent (range −0.8 to 2.2 Gm. per cent). Four of five depressed hematocrits rose, and seven exceeded control levels, the average level exceeding the control average by 1 per cent.

*Detailed laboratory data are available from the authors on request.

Mean corpuscular hemoglobin concentration fell in every case (average drop 2 per cent range 1 to 3 per cent) immediately after the last phlebotomy and remained depressed 1 to 3 months later Unfortunately control red cell counts were not available but immediate postexperiment counts were mildly depressed below the normal range in all 6 subjects on whom this test was performed By the time of the second determination 5 of these 6 subjects showed a rise in red count and in about one half of the total group the red count was within the normal range All subjects in Group I showed a slightly high or normal mean corpuscular hemoglobin and an abnormally high mean corpuscular volume on both the immediate and delayed determinations.

All subjects in Group II had normal hemoglobins and hematocrits and 3 of 4 had a normal red cell count 5 to 7 months after their last procedure Mean corpuscular hemoglobin concentrations were in the low normal range and mean corpuscular hemoglobins were in the high normal range Like their counterparts in Group I all subjects in Group II had elevated mean corpuscular volumes.

THROMBOCYTES. Platelet counts were normal in all subjects.

RENAL FUNCTION Except for the sporadic appearance of formed elements in the spun sediment urinalyses were normal in all subjects, as was the blood urea nitrogen The serum creatinine of one subject in Group I was mildly elevated (2.3 mg per cent) on the day after his last experiment but returned to normal on the follow up analysis. Serum uric acid levels were normal in all subjects in Group I initially but of them showed hyperuricemia on follow up examination as did two subjects in Group II Since urinalysis, blood urea nitrogen and serum creatinine levels were normal in these 4 subjects, the elevated uric acid is not considered to be a manifestation of kidney disease.

HEPATIC FUNCTION Liver function tests were within normal limits, except for an isolated abnormality in each of 3 subjects. One subject (D Z.) showed an elevated thymol turbidity of 5 2 units, another subject (D D) exhibited an increased cephalin flocculation of 3+/3+ for 24/48 hours, and a third subject (J L.) had a mildly elevated serum glutamic oxalacetic transaminase (SGOT) of 45 units. In each case every other liver function test was normal and therefore these isolated abnormalities have not been interpreted as indicating definite evidence of liver damage

Discussion

Although the incidence of complications after intravenous and intra arterial catheterization was significant only one variety of untoward reaction appeared to be enhanced by repeated catheterization Thus vasovagal reactions were rare after the first catheterization whereas irritation of the median nerve was unrelated to the number of procedures. The relationship of asymptomatic venous occlusion to the number of catheterizations was indeterminate, but the incidence of symptomatic thrombophlebitis was not enhanced by repeated cannulation. Arterial embolization on the other hand was definitely related to the number of times the vessel had been entered With one exception this complication arose when an artery was catheterized for the third time. The occurrence of this complication only after multiple catheterizations undoubtedly reflects an increased susceptibility to intra arterial clotting with repeated trauma to the endothelium It is of interest that the frequency of complications other than arterial was greatest during the first and second exposures. This undoubtedly reflects an improvement in experimental technique decreased anxiety of the subject and the elimination of some subjects as the project continued

Fortunately the complications in these subjects were not of significant consequence. The possibility exists however that serious problems could result from extensive thrombosis of the brachial artery with retrograde propagation of the clot or from multiple embolization to peripheral arteries. Furthermore all of the subjects in this study were young healthy men in whom only the arm vessels were cannulated A higher incidence of serious sequelae might be anticipated with repeated catheterization of the veins and arteries of the lower extremities, especially

in older individuals with pre-existing cardiovascular disease

Large losses of blood (up to liter in 7 months) were tolerated well with mild decreases in hemoglobin and hematocrit and subsequent return of these indices toward normal

Likewise the administration of large quantities of indocyanine green was tolerated without apparent local allergic manifestation or definite evidence of renal or hepatic dysfunction Previous studies indicate that this tricarbocyanine acid dye is innocuous in man and animal when used in doses of mg per kilogram or less The dye is probably bound to serum albumin and removed rapidly from the blood by the liver It is excreted somewhat more slowly into the bile in essentially unaltered form Little or no dye is eliminated by the kidneys. Although the recommended dose was not exceeded during any one experiment in this study the total dose in many cases was far in excess of 2 mg per kilogram (Table I) In view of the large total dosage and the repeated nature of administration one must consider the possibility that the dye was responsible for the transient neutropenia observed in 7 subjects. Especially surprising is the apparent depression of white cells in the subjects of Group I shortly after the removal of significant quantities of blood a procedure usually considered to be a stimulus to leukocytosis. A subsequent study has shown that repeated injection of indocyanine green in doses equivalent to those used in these studies does not cause leukopenia in the rabbit an animal chosen because of its predominant neutrophilic white blood count similar to that in man [12] Further investigation in human beings is warranted in order to confirm these animal experiments.

Summary and conclusions

Seventeen healthy male volunteers underwent one to seven arterial and venous catheterizations entailing the withdrawal of large quantities of blood and the injection of large amounts of indocyanine green over a 7 month period Immediate complications the status of arteries and veins and hematopoietic renal and hepatic function tests were analyzed after the study Vasovagal reactions were common during the initial exposure Irritation of the median nerve appeared to be unrelated to the number of catheterizations Thrombophlebitis occurred in 2 subjects after catheterization of the cephalic vein and asymptomatic venous occlusion occurred in 3 other subjects. Intra arterial thrombosis manifested by peripheral arterial embolization occurred four times and was observed only after multiple arterial cannulation

Removal of large quantities of blood was tolerated well with only mild decreases in hemoglobin and hematocrit levels and prompt return of these indices toward normal Clinical allergic reactions and definite laboratory evidence of renal or hepatic damage did not occur after the repeated administration of large doses of indocyanine green Transient unexplained neutropenia of mild to moderate degree was noted in 7 subjects whereas platelet counts were normal in all

It is concluded that (1) Catheterization of the arm vein in young healthy individuals is attended by a significant incidence of localized venous occlusion but the occurrence of symptomatic thrombophlebitis or serious sequelae does not appear to be enhanced by repeated cannulation (2) Repeated arterial catheterization may lead to an increased incidence of thrombosis and peripheral embolization. (3) Hepatic and renal function apparently do not suffer from the repeated administration of large doses of indocyanine green. (4) Further investigation is warranted in order to determine whether leukopenia is related to the administration of indocyanine green or whether the high incidence of leukopenia observed in this analysis is fortuitous.

REFERENCES

1 Hill A. B Principles of medical statistics New York, 1961 Oxford University Press pp. 260-263.
2 Zimmerman, H A editor Intravascular catheterization, Springfield, Ill 1959 Charles C Thomas, pp. 19-20 and 36-41.
3 Luisada, A. A editor Examination of the cardiac patient New York, 1965 McGraw Hill Book Co Inc Part 4 pp. 192 and 314 318
4 Fox, I J Brooker I G. S., Heseltine D W

Essex, H. E., and Wood, E. H. A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation, Proc. Staff Meet. Mayo Clin. 32:478, 1957
5. Hynson, Westcott & Dunning, Inc. Cardio-Green (CG) For cardiac research and diagnosis, Baltimore, 1965
6. Cherrick, G. R., Stein, S. W., Leevy, C. M., and Davidson, C. S. Indocyanine green. Observations on its physical properties, plasma decay and hepatic extraction, J. Clin. Invest. 39:592 1960.
7. Messer, J. V., Levin, H. S., and Pines, J.: Human cardiovascular performance during heat stress. Presented at the proceedings of the American Physiological Society, Los Angeles, Calif. August, 1965. Abstract in The Physiologist 8:233 1965
8. Levin, H. S., Messer, J. V., Pines, J., Murray, R. H., and Goldman, J. K. Cardiovascular respiratory and metabolic responses of man to cold, in abstracts of the 37th Scientific Sessions of the American Heart Association, Circulation 30: 113 1964
9. Seldinger, S. L. Catheter replacement of the needle in percutaneous arteriography. Acta Radiol. 39:368, 1953
10. Wheeler, H. O., Cranston, W. I., and Meltzer, J. I. Hepatic uptake and biliary excretion of indocyanine green in the dog. Proc. Soc. Exper. Biol. & Med. 99: 11 1958.
11. Wintrobe, M. M. Clinical hematology, ed. 5, Philadelphia, 1961 Lea & Febiger, pp. 250-252.
12. McDermott, P. H., Levin, H. S., Runco, V., Belcher, J., and Booth, R. W. Hematologic effects of repeated injection of indocyanine green in rabbits. Unpublished data.

Experimental and laboratory reports

Concealed digitalis-induced arrhythmias unmasked by electrical stimulation of the heart

Agustin Castellanos, Jr., M.D., F.A.C.C.
Louis Lemberg, M.D., F.A.C.C.
Manuel J. Centurion, M.D.
Burouk V. Berkovits, E.E.
Miami, Fla.

Cardiac arrhythmias produced by digitalis glycosides are well known in clinical electrocardiography and in experimental pharmacology. Less known, however, is the fact that digitalis-induced ventricular automaticity can be concealed.[1] Vagal stimulation, a method used to slow the natural ventricular rate by producing sinoatrial block or atrioventricular block, has been used experimentally in dogs to unmask digitalis-induced ventricular ectopic rhythms.[1] Exposure of these arrhythmias was made both prior to the appearance of spontaneous digitalis-induced tachycardias and also soon after their disappearance. The latent or subthreshold ectopic ventricular rhythm did not become manifest until, with increasing digitalis dosage, the rate exceeded that of the sinoatrial rhythm. It has been reported that electrical countershock may expose latent digitalis intoxication when used in terminating supraventricular arrhythmias, even when there had been no previous evidence of digitalis excess.[3] In addition, there have been some reports of instances in which electrical discharges of low intensity (pacemaker range[4]) and of high energies (countershock range) were able to unmask the toxic effects of cardiac glycosides at a time when they were not apparent in the electrocardiogram. The potential clinical implications promoted an experimental study to help determine whether electrical stimuli can systematically expose latent digitalis-induced arrhythmias.

Methods

Occult digitalis intoxication was studied in dogs subjected to pacemaking stimuli before and after digitalization. Ten mongrel dogs which weighed 10 to 20 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram intravenously). Ventilation was maintained with a Harvard pump. A flexible Teflon-coated 00 Surgaloy multistrand wire was introduced percutaneously into the heart and anchored to the ventricular wall. The wire, carried within a cardiac needle, has a 2-mm. hook at its proximal end. The needle was withdrawn after the ventricular cavity had been entered, and the wire was left attached to the endocardium. The wire was connected to the negative pole of the pacemaker. The positive pole was attached to a

From the Department of Medicine, Section of Cardiology, University of Miami School of Medicine and the Division of Electrophysiology, Jackson Memorial Hospital, Miami, Fla.
This study was aided by a grant from Florida Heart Association.
Received for publication May 27, 1966.
Address: Department of Medicine, University of Miami School of Medicine, Miami, Fla. 33136.
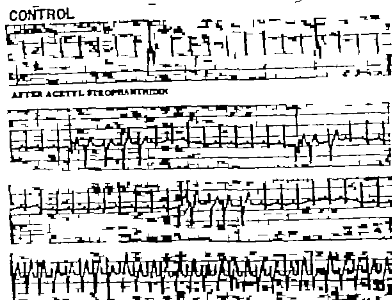


Fig. 1 Concealed digitalis arrhythmia unmasked by pacemaker stimuli. Diastolic pulses of threshold intensity produce single response during the control period. After the administration of acetyl strophanthidin, stimuli of similar intensity falling well after the end of the T waves are able to induce short runs of ventricular tachycardia (*second and third strip*). Thirty seconds later (*bottom strip*) spontaneous ventricular tachycardia appeared. The glycoside-induced beats had morphology similar to that of those produced electricall

needle inserted into a chest muscle of the animal

The instrument delivered impulses synchronized to the peak of a natural or an artificial QRS complex.[*] Either coupled or paired electrical stimulation could thus be applied. The pulses were slightly underdamped and had a duration of 2.5 msec. The pacemaker delivered voltages that ranged between 0 and 25 volts. A variable refractory period determined the number of artificial stimuli that could be delivered after any desired number of sinus impulses.

Test stimuli were initially administered in the late part of diastole of every ninth to fifteenth sinus beat. The intensity was progressively increased from zero until a threshold response was obtained. Then the intensity was adjusted so that it would vary between threshold values and two, six, and eight times threshold. The effects of stimuli *in these ranges on other parts of the ventricular* cycle (early diastole and relative refractory period) were also tested.

Acetyl strophanthidin was administered intravenously as a bolus at a dose of 1.0 μg per kilogram. As the pacemaker impulses occurred after every ninth to fifteenth sinus beat, the effects of artificial stimuli of varying intensity on the subsequent postextrasystolic pause could be monitored until a spontaneous arrhythmia appeared. The effects of stimuli delivered during systole and diastole were studied in all experiments. During digitalis-induced ectopic tachycardia impulses were also delivered after several natural beats. Immediately after the arrhythmia subsided the effects of pacemaker stimuli were also assessed in the manner described above. Pacing was discontinued when diastolic stimuli no longer elicited repetitive responses. The recording apparatus consisted of a direct writing electrocardiograph. Standard Leads I or II were recorded.

Results

Prior to the injection of acetyl strophanthidin pacemaker stimuli invariably produced only single extrasystoles even when falling during the expected vulnerable period. Digitalis-induced ventricular tachycardia occurred 2 to 6 minutes after the injection of the cardiac glycoside. This rhythm interfered with the basic sinoatrial pacemaker. The rates of the ventricular

[*] American Optical Company

tachycardias and sinoatrial rhythm were similar in the majority of the experiment. The QRS complexes were different in direction in Lead II but were not significantly prolonged in three cases. In one instance A-V nodal tachycardia occurred.

For approximately 1 minute before the appearance of the toxic arrhythmia, it was noted that the pause after the artificial extrasystoles was terminated by beats originating in ectopic centers (Fig. 1). These beats arose in the ventricles in all dogs except one in which they were A-V nodal in origin (Fig.). Generally the induced unexpected extrasystoles initially occurred late in diastole after the following T wave. A comparison of their morphology with that of those occurring later in the experiments revealed that they were fusion beats resulting from the simultaneous depolarization of the ventricles by supraventricular impulses and idioventricular pacemakers. Thereafter the number of poststimulation extrasystoles increased until the picture of a spontaneous ectopic tachycardia dominated the electrocardiogram. This phenomenon was observed in 9 dogs. During established ventricular tachycardia the diastolic artificial beats were seen to be followed by extrasystoles from another focus on three occasions (Fig. 3). Immediately after cessation of the glycoside-induced arrhythmias, all dogs again manifested the appearance of poststimulus ventricular (or in case A-V nodal) beats for a period of time ranging from 5 to 30 minutes. The number of extracontractions produced by each artificial stimulus *depended on their timing in relation* to the end of the glycoside-induced arrhythmias. Long runs of tachycardia

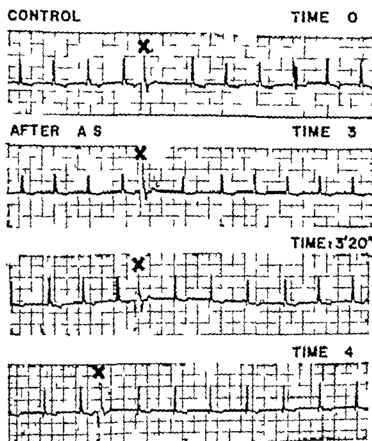


Fig. 2. Concealed nodal rhythm exposed by electrical stimulation. During the control period diastolic stimuli of threshold intensity (labeled X) produced a single response followed by a compensatory pause and then conducted sinoatrial beat. After acetyl strophanthidin the pause that followed diastolic stimuli of similar intensity was not terminated by a sinoatrial contraction but by isolated nodal beat (*second and third strips*) and by a run of A-V nodal rhythm (*bottom strip*).



Fig. 3. Concealed digitalis effects exposed by pacemaker stimuli. Repetitive firing occurring in response to diastolic pacemaker impulse of twice threshold intensity. This unusual response was seen 1 minute before the appearance of ventricular tachycardia induced by acetylstrophanthidin. During the latter event pacemaker stimuli elicit ventricular extrasystoles from another center.

after single stimuli were observed immediately after cessation of the glycoside induced arrhythmia. Thereafter the number of extrasystoles decreased progressively until the moment at which a single stimulus produced only the expected single response and the corresponding compensatory pause was ended by a conducted sinoatrial impulse.

The extrasystoles usually but not invariably (8 times out of 10) had the same morphology as that of those occurring during the spontaneous paroxysms. Since the secondary responses occurred well after the end of the T wave, vulnerability could be ruled out as the underlying mechanism. In 9 of 10 experiments the phenomenon under consideration could be induced with intensities as low as the ones required to produce a response in late diastole during the control period. During the latter period threshold values ranged between 1 and 1.5 volts. The ectopic beats occurred after stimuli delivered not only in diastole but in the responsive part of systole as well. Their number did not increase with higher energies (up to 25 volts).

When the last sinoatrial interval preceding the artificial stimuli was compared with the interval between the ventricular response induced by the stimulus artefact and the subsequent, unexpected ectopic beat the following results were noted. In all 10 dogs the basic ventricular cycle length was shorter than the first postextrasystolic pause. The reverse phenomenon also occurred in 5 of the dogs, that is, the duration of the interval from the first artificial extrasystole to the second ectopic beat was shorter than that of the basic sinus rate. This suggests that in the latter cases the extrasystoles were active and hence induced by the artificial stimuli.

Discussion

The exposure of latent digitalis toxicity by pacemaker stimuli has not been previously emphasized. Other procedures have been employed in unmasking digitalis intoxication at a time when there was no electrocardiographic evidence of toxicity. Rothberger and Winterberg[4] were the first to show that in dogs premedicated with strophanthidin a rapid ectopic rhythm could be unmasked by vagal stimulation. These investigations have been corroborated and extended by Vasalle and associates.[5]

Repetitive responses occurring after pacemaker stimuli were seen both during the responsive portion of systole and during diastole. Hence vulnerability could not be implied in the genesis of them. The intensity of the stimuli which evoked the multiple beats could be as low as the values which were considered to be threshold during the control period. At this time single stimuli elicited only one response even when falling in the vulnerable period. Thus, it seems that the repetitive firing threshold to single pacemaker stimuli was reduced throughout the responsive portion of the cycle. These results are in keeping with the work of Lown and associates, who postulated that the threshold to ventricular tachycardia produced by countershock

could be lowered considerably (in the range of 2,000 times) after digitalization. They found that ventricular tachycardia not related to the vulnerable period could be elicited with energies as low as 0.2 watt seconds.

As in the present report, the lowered threshold to electrical countershocks could occur even in the absence of overt manifestation of overdigitalization. It is proper, therefore, to say that electrical discharges either in the countershock or in the pacemaker range can indeed uncover a latent *digitalis-induced arrhythmia*.

The clinical significance of the present study is to suggest the possible diagnostic and in a way deleterious effects of pacemaker stimuli in some patients with borderline or overt digitalis toxicity. For instance, coupled and paired electrical stimulations are currently employed to augment cardiac output in failing hearts with ectopic tachycardia or sinus rhythm. This form of pacemaker therapy has been used in instances of glycoside-induced tachyarrhythmias. In the experiments presented in this report it was found that if true coupled stimulation (instead of delivering the testing stimuli after several sinoatrial beats) was started during sinus rhythm but soon after the disappearance of the digitalis-induced tachycardia, a bizarre arrhythmia would result (Fig. 5). This arrhythmia ceased when coupled stimulation was discontinued. It is possible that a similar reaction could occur in patients who are receiving large amounts of digitalis, but who are still in sinus rhythm at the time at which electrical stimulation is initiated.

The exposure of digitalis toxicity by pacemaker stimuli can be explained in several ways. At times the R-R interval of the sinus rate is shorter than the interval between the first and the second (unexpected) ectopic beats. If a latent pacemaker is present with a rate just below that of the sinoatrial node, it can become apparent after a prolonged pause. However, this mechanism does not explain those experiments in which an extrasystole followed the first artificial beat at a shorter interval than that of the basic sinoatrial rate. Vulnerability was ruled out because the stimulus was given after the relative refractory period.

A possibility to be considered is that a pacemaker stimulus may lower the threshold of excitability in the digitalized heart. It has been shown by Moe and Mendez[19] that digitalis lowers the threshold of excitability at a time when spontaneous arrhythmias appear. Subsequently, the threshold increases, with added increments of glyco-

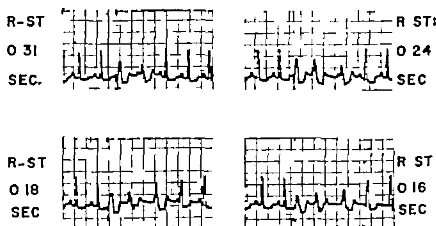


Fig. 4. Concealed digitalis arrhythmia unmasked by pacemaker stimuli. Numbers indicate intervals between the peak of the R wave and the pacemaker stimulus artefact. During the control period single stimuli produced only one response. A ventricular tachycardia appeared 5 minutes after the injection of acetylstrophanthidin. Immediately after disappearance of the latter arrhythmia single impulses of control threshold intensities induced multiple responses. The QRS complexes were almost identical to those seen during the glycoside-induced tachycardia. The peculiar form of sensitivity in the digitalized dogs was not related to any specific portion of the heart cycle. Therefore, vulnerability could not be implicated as the underlying mechanism.

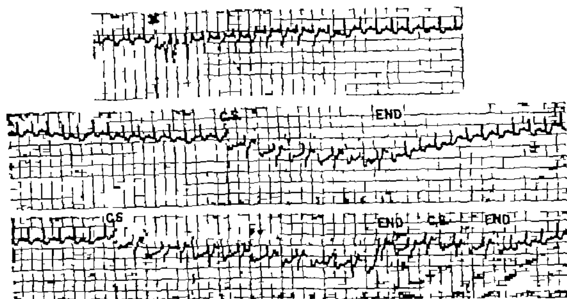


Fig. 5. Concealed digitalis effects exposed by pacemaker stimuli. Arrhythmia produced by coupled electrical stimulation. A few minutes after cessation of the arrhythmia induced by acetyl strophanthidin, single diastolic pacemaker stimulus reinduces the glycoside-induced tachycardia. Coupled stimulation started at this moment resulted in a bizarre arrhythmia. Each pacemaker stimulus was followed by an ectopic ventricular contraction. The arrhythmia disappeared when coupled stimulation was discontinued.

sides approaching the lethal dose. Moreover, the experiments performed by Lown and co-workers[7] have implied that digitalis indeed lowers the threshold for countershock-induced ventricular tachycardia. Although the relationship between the ventricular tachycardia threshold and the *diastolic threshold* on the one hand and the ventricular fibrillation threshold (due to *vulnerability*) on the other hand is far from clear, there is preliminary evidence to support the assumption that cardiac glycosides at one moment or another are able to lower the various thresholds of excitability.[3,18]

It should be noted that during the testing period, i.e., immediately before the appearance and shortly after the disappearance of ventricular tachycardia induced by acetyl strophanthidin, the Purkinje fibers could well have an increased automaticity. The latter is considered to be a consequence of the digitalis-induced enhanced diastolic depolarization during Phase 4, as shown by Hoffman and Singer in cellular recordings.[12] The enhanced diastolic depolarization begins before there are overt changes in driven action potentials and further shortening occurs until multifocal activity is present. The combination of a drug and pacemaker induced lowered threshold (Wedensky effect[13]) and a glycoside-enhanced diastolic depolarization can explain the premature ectopic beats that occur only after pacemaker stimuli.

The possibility that electrical currents can lower the threshold to cardiac stimulation in the absence of previous digitalization has long been considered. As far back as 1886, Wedensky[13] found that in the nerve muscle preparation the muscle failed to respond if the nerve was stimulated by subthreshold stimuli. When a strong induction shock was applied to the nerve so that a muscular contraction occurred, the previous subthreshold stimuli were then able to elicit responses. The Wedensky phenomenon was later demonstrated in the dog's heart by Goldenberg and Rothberger. Recently, Castellanos and associates[4] were able to show that this phenomenon could occur in the human heart. In patients with complete A-V block and slow idioventricular rhythms, electrical stimuli were delivered from two separate pacemakers. The stimuli from one instrument provided currents with subthreshold intensity. Strong shock (15 times above threshold) delivered with the second pacemaker enabled the heart to respond to

previous subthreshold stimuli Since the electrical stimuli did not fall during the vulnerable period or the supernormal period the Wedensky phenomenon could thus be the underlying mechanism This mechanism can also be operating in patients with artificial pacemakers and latent digitalis intoxication

Trautwein and Kassebaum[15] have also shown that weak constant electrical currents can increase the slope of diastolic depolarization in Purkinje fibers hence initiating ectopic pacemaker activity

Lown and associates[7] considered that the appearance of cardiac arrhythmias after low-energy countershocks in digitalized dogs was due to a loss of potassium from the cell The loss of potassium induced by digitalis could very well lower the threshold for the electrically induced tachycardia As an alternative explanation they suggested that the shock could have injured the membrane hence re-triggering digitalis intoxication Sarnoff and associates[16] have reported that pacemaker stimuli delivered as paired electrical stimulation result in a loss of cellular potassium Thus when the heart is in precarious potassium balance and has been subjected to nearly toxic digitalization single electrical stimuli can induce arrhythmias by transiently lowering cellular potassium This explains the mechanism whereby electrical stimuli may expose latent digitalis toxicity

Summary

The relationship between the action of acetyl strophanthidin and pacemaker stimuli was studied experimentally In all animals, single pacemaker impulses were able to induce repetitive firing immediately before the appearance of the glycoside induced tachycardia as well as up to 30 minutes after its disappearance Thus phenomenon was seen with impulses falling in any part of diastole as well as in the responsive portion of systole Hence vulnerability could be ruled out as the underlying mechanism The intensities required for repetition were as low as control threshold values. It appears that electrical stimuli with intensities in the range of those used in commercially available pacemakers can unmask concealed digitalis toxicity

It is possible that this peculiar type of sensitivity to pacemaker stimuli in digitalized animals could be due to a loss of cellular potassium induced by the electrical discharge

REFERENCES

1 Vassalle M and Greenspan, K. Concealed ventricular automaticity during ouabain administration, Circulation 24 1061 1961
2 Vassalle M Greenspan, K., and Hoffman B F: Analysis of arrhythmia induced by ouabain intact dogs, Circulation Res 13 132, 1963.
3 Vassalle M and Greenspan, K. L. Effect of potassium on ouabain induced arrhythmias, Am. J Cardiol. 12:692, 1963
4 Rothberger C. J and Winterberg, H.: Über den Einfluss von Strophantin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens Pflüger Arch 150:217 1913.
5 Gilbert R and Cuddy R. P. Digital intoxication following conversion to sinus rhythm, Circulation 32:58, 1965
6 Castellanos, A J Lemberg L., Johnson, D and Berkovits, B V The Wedensky effect in the human heart, Brit H rt J 28:276, 1966.
7 Lown, B Kleiger R and Williams, J Cardioversion and digitalis drugs Changed threshold to electric shock in digitalized animals, Circulation Res 17 519 1965
8. Conference on Paired Pulse Stimulation and Postextrasystolic Potentiation of the Heart. Parts I and II B II New York Acad. Med. 41 Nos. 5 and 6, 1965
9 Vassalle M Karis J and Hoffman, B. F. Toxic effect of ouabain on Purkinje fibers and ventricular muscle fibers, Am. J Physiol. 203:433 1962.
10. Moe G. K., and Mendez, R. The action of several cardiac glycosides on conduction velocity and ventricular excitability in the dog heart, Circulation 4 729 1951
11 Grondin, P Lepage G Guignard, J and Karamehmet, A. Evaluation of cardiac drugs in the presence of electrical pacemaker J Thorac. & Cardiovas. Surg 41:911 1961
12. Hoffman B. F and Singer D : Effects of digitalis on electrical activity of cardiac fibers, Prog. Cardiovas. Dis. 7:226, 1961
13 Wedensky N P Über die Beziehung zwischen Reizung and Erregung in Tetanus, Ber Akad Wiss. St. Petersburg 51:96, 1886.
14 Goldenberg M and Rothberger C J Untersuchungen an der spezifischen Muskulatur des Hundeherzens, Ztschr ges. exper Med. 90:508, 1933.
15 Trautwein, W and Kassebaum, D G.: On the mechanism of spontaneous impulse generation in the pacemaker of the heart, J Gen. Physiol 45:317 1961
16. Sarnoff S J Gilmore J P Daggett W M Mansfield, P B McDonald, R. H., Jr and Weisfeldt M L Net potassium loss and changes in oxygen and ventricular performance during paired stimulation of the heart, Bull New York Acad. Med. 41:602, 1965.

Vascular patterns in the canine sympathetic chain

Hermit Q. Mc carian, M.S., Ph.D.
Thomas B. Jenkins, M.S., Ph.D.
East Lansing, Mich.

The sympathetic chain as a portion of the autonomic nervous system has received much attention by anatomists and physiologists with regard to its structure and function; however, little attention has been paid to the fact that it is in the literal sense an organ and therefore dependent upon the cardiovascular system for its blood supply. In order that the sympathetic nervous system influence the blood supply to various areas of the body, the sympathetic chain must itself be supplied with blood to perform this regulatory function.

Unfortunately, little work has been done on the vascular patterns of the sympathetic chain. The earliest studies on the vascularization of the sympathetic chain were reported by Delamere and Tanasesco, Anserow, and De Souza. Adams gave a historical review of the blood supply to nerves, in which he discussed all previous work on the blood supply to the sympathetic chain. Patterson[11,12] described the sources of arterial blood supply to the cervical and stellate ganglia of new-born infants. Chungcharoen and associates[3] studied the blood supply of the superior cervical sympathetic and nodose ganglia in cats, dogs, and rabbits.

This paper presents a description of the intrinsic vascular patterns in the thoracic, lumbar, and sacral portions of the canine sympathetic chain.

Materials and methods

Fifteen dogs were anesthetized with pentobarbital sodium (25 mg. per kilogram) via the cephalic vein. The common carotid artery and external jugular vein were cannulated. Infusion by gravity (4 feet) of warm heparinized saline (0.85 per cent NaCl plus 0.5 per cent heparin) via the external jugular vein was begun simultaneously with exsanguination through the common carotid artery. The saline solution was warmed to body temperature (38°C.) because preliminary trials with cold saline killed other animals before the infusion was completed. Infusion was continued until clear saline flowed from the common carotid artery, at which point the infusion of saline was stopped and the infusion of warmed Pelikan India ink† was started. The infusion of India ink was continued for about 1 to 2 minutes after the eyes, gums, and tongue were totally blackened. After death the specimens were refrigerated until they could be eviscerated and submerged in 10 per cent formalin.

After the fixation, the two sympathetic chains from T to the sacral regions, their surrounding blood vessels, and tissues were

From the Department of Anatomy, College of Veterinary Medicine and College of Human Medicine, Michigan State University, East Lansing, Mich.
This investigation was supported by Michigan State All-University Grants No. [illegible] and No. [illegible].
Received for publication May [illegible].
*Present address: Department of Anatomy, School of Medicine, The Creighton University, Omaha, Neb. [illegible]
†John [illegible] and Co., Inc., 425 Park Ave. South, New York 16, N. Y.

dissected out intact. The intrinsic vessels thus could be traced back to previously identified arteries and veins when necessary.

The dissected tissues were then reduced to 3 inch square sections, dehydrated in three changes of acetone (30 minutes each) and cleared in methyl benzoate. This procedure cleared the sympathetic chain and surrounding connective tissue and permitted a stereoscopic study of the infused intrinsic vascular pattern of the chain.

The cleared tissues, submerged in a Petri dish filled with methyl benzoate, were studied with the aid of a Bausch and Lomb dissecting microscope (Model RD 815) at magnifications of 10, 30, and 60 times. It was important to use a dissecting microscope of this type in order to get the best illumination and stereoscopic visualization of the injected blood vessels, i.e., direct light passed down through the specimen from a surgical lamp and reflected light passed upward through the specimen from the substage mirror. The cleared tissues were kept submerged in methyl benzoate throughout the course of this study because they dried out rapidly and became undissectible when exposed to the air.

Photomicrographs of the tissues cleared in methyl benzoate were taken with a Leica 111 g 35 mm. camera which was attached to an Ipso 1.3x intermediate adapter.* One eyepiece of a Bausch and Lomb binocular dissecting microscope (Model RD 815) was removed and the Ipso adapter (with 10x ocular) and camera were mounted on the microscope. The photomicrographs were necessarily taken of tissues submerged in methyl benzoate. A glass histologic slide was placed over the tissues in order to keep them stationary while being photographed. Kodak high-contrast copy film was used and the film was developed in Neofin rot.

Results

Interganglionic chain. Vascular patterns common to both the arteries and veins of the interganglionic chain will be discussed simultaneously in order to avoid duplication. Differences between the arterial and venous patterns will be noted whenever present. The following characteristics were used to distinguish arterioles from venules: (1) The diameter of the venules is greater than that of their corresponding arterioles. (2) The arterioles usually branched dichotomously, whereas several tributaries united to form a venule. (3) The arterioles gave off fewer perpendicular side branches than did the venules. (4) Venule-venule anastomoses were more numerous than arteriole-arteriole anastomoses. (5) The venules were usually more tortuous than the corresponding arterioles.

The major interganglionic vessels were generally arranged parallel with the long axis of the sympathetic chain (Figs. 1 and 3). The blood vessels were placed into three categories on the basis of the order of size and location in the chain, namely, epineural vessels, perineural vessels, and endoneural vessels.

EPINEURAL VESSELS (FIGS. 1 AND 4). The epineural vessels were the largest interganglionic vessels. The arterioles were usually accompanied by a corresponding venule, the caliber of the venule being approximately 2 to 3 times greater than that of the arterioles (Fig. 4). In no case did an epineural arteriole appear to have a greater diameter than its concomitant venule.

Two sets (an arteriole and its corresponding venule constitute a set) of longitudinal epineural vessels were present, one in the medial and one in the lateral epineurium of the chain (Figs. 1 and 4). The arteriole was usually directly dorsal to the venule and intimately bound to the latter by connective tissue. Since the venule was larger, the arteriole was frequently hidden by the venule in the India ink preparations; however, it was not uncommon to see the the two vessels coursing side by side in the epineurium (Fig. 4). Occasionally, direct longitudinal branches from the epineural vessels or short perpendicular branches which immediately divided into ascending and descending longitudinal rami formed multiple epineural vessels. Multiple epineural venules were more common than arterioles.

Superficial transverse anastomotic channels connected the medial and lateral epineural vessels at irregular intervals (Figs. 1, 2, 4, and 5). The caliber of these anastomotic channels varied considerably, some

*Tetenal-Photowerk, Hamburg, Germany.



Fig. 1. A surface view of the interganglionic chain at L, showing two transverse venous anastomoses. Cleared in methyl benzoate. ×43.



Fig. 2. A surface view of the interganglionic chain at T. The epineural arteries are hidden by the veins. Note the venous loop and the perineural venule draining into the transverse channel. Cleared in methyl benzoate. ×78.

were the same size as the parent vessel whereas others were only capillaries. The larger transverse channels gave off perpendicular branches which either penetrated the deeper portions of the chain or remained superficial (Fig.).

Anastomosing venular networks drained into the epineural veins (Figs. 4 and 5). These superficial networks, which were especially prominent in the thoracic levels, covered only the medial and lateral borders of the epineurial surfaces of the chain. The middle portion of the chain's dorsal and ventral surfaces was usually devoid of venous networks, except for occasional transverse connections between the medial



Fig 3 A surface view of the interganglionic chain at T₆, showing the longitudinal arrangement of the endoneural vessels. The epineurium has been dissected away. Cleared in methyl benzoate ×86.



Fig 4 A surface view of the interganglionic chain at T showing the epineural arterial and venous arcades. Note the transverse anastomosis. This specimen has not been dissected hence the central portion appears clear. Cleared in methyl benzoate; ×44

and lateral networks. A well-defined longitudinal line of venular loops usually separated the arcades from the middle surfaces of the chain in the thoracic region (Figs. 4 and 5). This demarcation became less definite at progressively lower levels of the chain consequently the transverse connections between the medial and lateral networks became more numerous. The anastomosing venular nets occasionally encircled the epineurium of the vagosympathetic trunk as one continuous longitudinally directed network. From the morphologic appearance it may be presumed that the



Fig. 5. Higher-power view of Fig. 4 showing an A-V anastomoses between the transverse channels. Cleared in methyl benzoate. X90.

epineural venules drain into three general areas of the venous circulation, namely (1) the segmental veins, (2) the venae vasorum, and (3) the veins of adjacent tissues.

1. Segmental Veins. The larger venules of the thoracic chain drained into nearby intercostal veins. The venules of the lumbar region drained into the lumbar veins and the veins of the surrounding muscles. In the sacral region the venous drainage passed into the sacrospinal veins and the median sacral vein.

2. Venae Vasorum. The smaller venules of the thoracic chain which were located approximately midway between the intercostal veins drained into the azygous vein or venae vasorum of the aorta and inferior vena cava. In the lumbar region the smaller venules drained into the venae vasorum of the inferior vena cava and aorta, whereas in the sacral region venous drainage was into the venae vasorum of the median sacral artery and median sacral vein.

3. Veins of Adjacent Tissues. The smallest venules of the thoracic, lumbar, and sacral chains, including some tributaries of the venous arcades, appeared to drain into the venous networks of the connective tissue adjacent to the sympathetic trunk; however, a functional study may show the reverse to be true.

PERINEURAL VESSELS. The perineural vessels were perpendicular branches of the epineural vessels which penetrated the perineurium of the chain and divided into ascending and descending longitudinal channels (Figs. 1 and 2). These vessels were further reduced in caliber either by dichotomous divisions or by giving off short perpendicular branches which immediately divided into ascending and descending longitudinal rami. The perineural vessels exhibited no significant anatomic features other than being transitional vessels from the arterioles and venules to the capillary level.

ENDONEURAL VESSELS (FIGS. 1-3). The endoneural vessels were the smallest vessels in the sympathetic chain. They cannot all be regarded as being capillaries since arterioles and venules were seen in the endoneurium. Perpendicular branches from the perineural vessels divided into ascending and descending rami to form the longitudinally directed capillaries. These longitudinal branches anastomosed with other ascending and descending rami to form continuous longitudinal networks throughout the interganglionic chain. Capillaries divided dichotomously, each branch anas-

tomosing with an adjacent ramus to form rectangular longitudinally directed meshes. Occasionally the dichotomously dividing rami reunited farther along the ramus reforming the original longitudinal capillary. In some cases adjacent capillaries anastomosed with the loop formed by the reuniting rami whereas in others they did not.

Here again as with the epineural and perineural vessels, the structural configuration of the capillaries makes possible numerous collateral pathways.

Ganglia. The vascular patterns in the ganglia of the thoracic, lumbar, and sacral portions of the sympathetic chain were sufficiently similar to be grouped together and discussed simultaneously. Specific differences between them, however, will be noted whenever present.

THORACIC, LUMBAR, AND SACRAL GANGLIA. The vascularity of the ganglion was approximately three to four times greater than that of the interganglionic chain (Figs. 6 and 7). This supports the assumption of Dunning and Wolff that there is a quantitative relationship between vascularity and metabolic activity in the nervous system. They showed that nervous tissue containing synapses was more vascular than nervous tissue without synapses.

The arterial supply to the ganglia was furnished by two sets of vessels. The vessels of the first category were direct branches from the aorta, intercostal, and lumbar arteries, whereas those of the second category were longitudinal continuations of the intrinsic vasculature in the interganglionic chain and spinal nerve.

The extrinsic vessels usually approached the ganglia from the cranial and caudal borders of the ganglia. It was not uncommon, however, for the smaller arterioles to penetrate any border of the ganglia. The extrinsic vessels supplied the ganglia in three ways. First, arterioles ramified on the surfaces of the ganglia to form a superficial vascular network. Perpendicular rami from this network penetrated to the interior of the ganglia. Second, arterioles at the poles of the ganglia immediately entered the deeper portions of the ganglia and anastomosed with the penetrating surface vessels. Occasionally these arterioles bifurcated, one branch ramifying on the ganglionic surface and the other passing centrally into the ganglion. Third, as arterioles from the poles coursed along the medial extent of the ganglion and continued as epineural arteries in the interganglionic chain, perpendicular rami were sent to the superficial and deep ganglionic networks.

The extrinsic ganglionic vessels were derived primarily from the longitudinal continuations of the interganglionic vasculature (Fig.). The epineural arteries either gave off perpendicular rami to the ganglion as they passed over it or bifurcated, one branch continuing as the epineural artery and the other supplying the ganglion. The perineural and endoneural vessels reached the deeper portions of the ganglion and anastomosed with the pre-existing vessels. The vasa nervorum of the spinal nerves also contributed blood vessels to ganglia in a similar manner.

Only occasionally do venules accompany the extrinsic ganglionic arterioles. The superficial venous networks of the interganglionic chain continued on to the ganglia. Usually, the lateral venous networks of the chain became confluent in the region of the ganglia, forming a complete periganglionic venous network.

The chain ganglia presented a characteristic venous pattern (Figs. 6 and 7). Numerous venous tributaries converged upon relatively larger vessels in the deeper portions of the ganglion. Four to ten intraganglionic venules united to form still larger venules at the surface of the ganglion. The superficial tributaries converged into two to four large efferent channels of each ganglion. The latter usually drained into the nearest available veins, viz., intercostal, lumbar, or sacral veins. The lumbar ganglionic veins occasionally drained into adjacent muscular tributaries.

The largest and most constant efferent channel of each thoracic ganglion drained laterally into a corresponding segmental vein. This vessel originated on either the dorsal or ventral surface of the ganglion. In the instances in which this vessel was not present, two smaller veins, one on the dorsal and one on the ventral ganglionic surface, were situated in a comparable position. The lumbar ganglia, being more fusiform than the thoracic ganglia, fre-



Fig 6 A surface iew of T ganglion showing ein draining the ganglion and interganglionic chain from the medial (aortic) side of the ganglion. Cleared in methyl benzoate ×30



Fig 7 A surface view of T ganglion showing the greater ascularity of the ganglion (G) compared t the in erganglionic portion at the right. Cleared in methyl benzoate ×13

quently showed two major vein which appeared to dominate the venous drainage n their respective halves of the ganglia. This pattern wa more common n the lower lumbar ganglia.

The second most constant vein of the thoracic g nglion drained medially into an intercostal vein Th essel was u ually smaller n diam ter than the lateral vein Commonly nterganglionic vein d ned nto the medial and later l g nglionic veins (Fig 6) Major efferent hannel wer not uncommon on the cr nial nd udal sur faces of the g nglion Numerous eno-



Fig 8 A higher-power view of Fig 7 showing arterial and venous patterns of the ganglion. The bifurcating arteriole to the left of the ganglion shows one branch penetrating the ganglion and the superficial branch sending perpendicular rami to the ganglion as it continues to the interganglionic chain. Note the A V anastomoses. Cleared in methyl benzoate. ×38.

venous anastomoses were observed in the ganglionic vessels.

In agreement with the findings of Mizeres short horizontal connecting filaments were present between the corresponding ganglia of each side in the sacral region. Anastomoses of the adjacent ganglionic vascular plexuses occurred through these horizontal filaments. Occasionally the adjacent sacral ganglia were completely fused in the midline. These fused ganglia had independent extrinsic blood vessels there was a common intraganglionic vascular plexus.

The arteriovenous anastomoses described by Nonidez[10] were commonly seen in the sympathetic ganglia (Fig 8). These anastomoses were occasionally observed in the interganglionic chain (Fig 5).

Discussion

The angioarchitecture of the canine sympathetic chain leads to a great deal of speculation about the functional significance of these vessels. Roberts[11] observed extensive degeneration of the axons in the sciatic nerve of dogs when the epineural vessels were stripped away. He further stated that the longitudinal anastomoses within the sciatic nerve were inadequate for maintaining nourishment to the nerves. Our observations indicate that the anastomosing nature of intrinsic vasculature to the chain could sufficiently compensate for localized deficiencies in the extrinsic arteries, whereas extensive occlusions of the regional arteries in more than four or five segmental levels of the chain would probably result in ischemia in the sympathetic chain. This theory is in agreement with that of Bacsich and Wyburn who inferred that the longitudinal networks within a nerve were capable of maintaining the normal flow of blood in a nerve after experimental crush injury to the nerve.

The transverse capillary anastomoses normally may not be functional however if the circulation to a particular portion of the chain were impaired the capillary anastomoses could enlarge to form compensatory collateral vessels. This theory is consistent with the findings of Bellman and associates, who stated that large collateral vessels usually develop from small preexisting bridging pathways in vascular beds before occlusion.

The significance of A V anastomoses in the chain may be attributed to the irregu-

lar functioning of the sympathetic nervous system. If sympathetic excitation is minimal, the metabolic activity in the chain is as low as is the need for capillary exchange. Consequently, the A-V anastomoses remain open to shunt the blood directly into the venous circulation. On the other hand, when sympathetic excitation is great, the metabolic activity in the chain increases and the A-V anastomoses close to let the blood flow through the capillaries.

Summary

The vascular patterns in the sympathetic chains of 15 dogs were studied by means of infusions of Pelikan India ink.

The interganglionic vessels were generally arranged parallel to the long axis of the chain. The blood vessels were divided into three categories, on the basis of the order of size and location in the chain, namely, epineural vessels, perineural vessels, and endoneural vessels.

The vascularity of the sympathetic ganglia was approximately three to four times greater than that of the interganglionic chain.

Arteriovenous anastomoses were commonly seen in the chain and their possible functional significance has been discussed.

REFERENCES

1. Adams, W. E.: The blood supply of nerves. I. Historical review, J. Anat. 76:323, 1942.
2. Anserow, N. I.: Die Arterien des Ruckenmarks, der Intervertebralganglien und der sympathischen Ganglien, Anat. Ber. 3:348, 1925.
3. Bacsich, P., and Wyburn, G. M.: The vascular patterns of peripheral nerve during repair after experimental crush injury, J. Anat. 79:9, 1945.
4. Bellman, S., Frank, H. A., Lambert, P. B., and Roy, A. J.: Studies of collateral vascular responses, Angiology 10:214, 1959.
5. Chungcharoen, D., de Burgh Daly, M., and Schweitzer, A.: The blood supply of the superior cervical sympathetic and the nodose ganglia in cats, dogs, and rabbits, J. Physiol., London 118:528, 1952.
6. Delamere, G., and Tanasesco, J. C.: Étude sur les artères du sympathique céphalique, cervical, thoracique et abdominal, J. Anat. Paris 42:98, 1906.
7. De Souza, O. M.: Contribution à l'étude de la vascularization du système nerveux organo-végétatif, Ann. Anat. Path. méd-chir. 9:975, 1932.
8. Dunning, H. S., and Wolff, H. G.: The relative vascularity of various parts of the central and peripheral nervous system of the cat and its relation to function, J. Comp. Neurol. 67:433, 1937.
9. Mizeres, N. J.: The anatomy of the autonomic nervous system in the dog, Am. J. Anat. 96:285, 1955.
10. Nonidez, J. F.: Arterio-venous anastomoses in the sympathetic chain ganglia of the dog, Anat. Rec. 82:593, 1942.
11. Patterson, E. L.: Sources of arterial blood supply to the superior and middle cervical sympathetic ganglia and the ganglion intermédiaire, J. Anat. 84:329, 1950.
12. Patterson, E. L.: The arterial supply to the stellate ganglion, J. Anat. 87:212, 1953.
13. Peterson, R. A., Ringer, R. K., Tetzlaff, M. J., and Lucas, A. M.: Ink perfusion for displaying capillaries in the chicken, Stain Tech. 40:351, 1965.
14. Roberts, J. T.: The effect of occlusive arterial diseases of the extremities on the blood supply of nerves. Experimental and clinical studies on the role of the vasa nervorum, Am. Heart J. 35:369, 1948.

The hemodynamic effects of diphenylhydantoin

Robert D. Conn, M.D.
J. Ward Kennedy, M.D.
John R. Blackmon, M.D.
Seattle, Wash.

Evidence has recently accumulated to show that diphenylhydantoin (DPH) is an effective antiarrhythmic agent. Several investigators have found that, when used parenterally, DPH is effective against both supraventricular and ventricular arrhythmias, particularly those resulting from digitalis toxicity. In addition, when used orally, DPH has been shown to be highly effective against a variety of recurrent arrhythmias. These reports have stimulated the widespread empirical use of this agent for cardiac arrhythmias even though its effects on the cardiovascular system of patients have not been well established. This report records observations on the hemodynamic effects of clinical doses of DPH in 12 patients studied during routine cardiac catheterization.

Methods

Twelve patients were studied during routine cardiac catheterization without general anesthesia or premedication. The clinical diagnoses are listed in Table I. None of the patients had congestive heart failure at the time of the study, and all were in sinus rhythm except Patients 1 and 3, who had atrial fibrillation. Data on pressure and flow were acquired through a catheter in the pulmonary artery and either a catheter in the aorta or a needle in the radial artery. Pressures were obtained through Statham P23Db strain gauges and recorded on a Sanborn 550M multichannel optical recorder. Mean pressures were acquired through electronic integration of the aortic, radial, or pulmonary arterial pressure curves. Systemic resistance was calculated as the ratio of mean systemic blood pressure to cardiac output. Cardiac output was measured by dye-dilution techniques, using indocyanine green as the indicator. Five milligrams of indocyanine green was injected into the pulmonary artery from a calibrated syringe. Blood was then withdrawn through a Waters X 250 densitometer system at a constant rate of 38.2 ml. per minute. Indicator-dilution curves were inscribed on a Leeds and Northrup Type 6 recorder. Calibration of the densitometer was carried out after inscription of each set of curves by passing a known quantity of green dye diluted in a blank specimen of the patient's arterial blood through the densitometer system. Cardiac output was then calculated by the Stewart and Hamilton principle. Patients whose initial dye-dilution curves were not of good quality were not used as test subjects. The electrocardiogram was recorded as a Standard Lead II on the Sanborn 550M recorder.

After catheters and arterial needles had

From the Department of Medicine, Division of Cardiology, University of Washington, Seattle, Wash.
Received for publication May [illegible], 1966.
*Teaching and Research Scholar of the American College of Physicians. Address: Department of Medicine, University of Washington School of Medicine, Seattle, Wash., 98105.

been appropriately placed and the patient appeared to be relaxed base-line determinations of pulmonary arterial pressure systemic arterial pressure and the electrocardiogram were obtained Three dye dilution cardiac output curves were then recorded in rapid succession. Two hundred and fifty milligrams of DPH sodium diluted in 5.0 ml of standard diluent was then injected into the pulmonary artery in 3 to 5 minutes and was flushed with 30 ml. of normal saline. Recordings of pressure were made continuously for 6 to 8 minutes after the administration of DPH except during the time that cardiac output was measured Dye-dilution curves were then recorded at 3 4 and 5 minutes after the injection of DPH Each of the hemodynamic variables acquired before and after DPH were analyzed by the Wilcoxon signed rank test for paired data. The electrocardiograms were analyzed immediately prior to the injection of DPH and at intervals for the first 7 minutes after injection.

Results

Table I summarizes the data acquired on the 12 patients in this study Intravenous injection of 250 mg of DPH (2.5 to 5.4 mg per kilogram) did not result in significant changes in cardiac output systemic or pulmonary arterial pressures heart rate peripheral resistance or stroke volume Analysis of the electrocardiogram before and after DPH revealed no changes in the P R interval QRS or ST T segments, with the exception of one patient whose T waves were negative before but positive after DPH

Five of 12 patients developed paroxysms of coughing associated with a substernal burning sensation during the administration of DPH into the pulmonary artery This response occurred despite slow injection with frequent saline flushing and ceased with the termination of the injection.

Discussion

Prior to 1963 several investigators found that DPH would abolish a variety of experimentally induced cardiac arrhythmias Toxic effects were noted but there were few systematic studies of the cardiovascular effects of this agent. Harris and Kokernot[4] found that doses of 12.5 mg per kilogram injected rapidly produced transient but significant hypotension in dogs. The same dose given slowly ($4\frac{1}{2}$ minutes) resulted in only slight alteration of the blood pressure Larger doses (20 mg per kilogram) when given rapidly resulted in cardiac and respiratory arrest although doses up to 50 mg per kilogram were well tolerated when given slowly Mosey and Tyler[5] compared the effects of DPH with those of procainamide procaine, and quinidine in digitalis-induced arrhythmias in dogs but hemodynamic data were not obtained The antiarrhythmic effects were similar for each agent although the effective dose of DPH (10 to 30 mg per kilogram) was slightly less than that of quinidine and procainamide (10 to 40 mg per kilogram) The duration of action of DPH did not differ significantly from that of quinidine and procainamide Second-degree heart block was produced by both DPH and procainamide Excitability of the central nervous system was noted with the use of quinidine and procaine but not with DPH or procainamide Scherf and associates[18] found that DPH was effective against atrial arrhythmias induced by aconitine and delphinine Hemodynamic measurements were not made in this study although cardiac toxicity in the form of atrioventricular block and interference dissociation was observed More recently Lang and associates using an autotransplanted heart-lung and cerebral venous shunt preparation demonstrated that the antiarrhythmic effects of DPH were due to its direct action on the heart, and not mediated through reflexes from the central nervous system In a similar manner Mixter and associates studied the cardiac and peripheral vascular effects of DPH in animals with divided circulations. DPH was found to directly depress myocardial contractility and to possess potent peripheral vasodilating effects. Evidence was also presented to suggest that reflex cardiac depression resulted from exposure of the peripheral vasculature to DPH Gupta and associates in an evaluation of the effect of DPH on the coronary and systemic circulations in dogs found that the drug increased coronary

Table I Hemodynamic and electrocardiographic data before and after intravenous diphenylhy

Patient	Diagnosis	Dose of DPH (mg per Kg)	Cardiac output (L/min) Before	Cardiac output (L/min) After	Mean arterial pressure (mm. Hg) Before	Mean arterial pressure (mm. Hg) After	Total peripheral resistance (dynes sec cm) Before	Total peripheral resistance (dynes sec cm) After	Mean pulmonary arterial pressure (mm Hg) Before	Mean pulmonary arterial pressure (mm Hg) After
1	Rheumatic he rt disease aortic tenosis nd insufficiency	3 3	4 9	5 0	80	88	1 300	1 400		
2	Rheumatic he rt disease mitr l regurgitat n	1 3	6 4	6 6	79	75	990	910	14	13
3	Rheumatic heart dise se m tral stenosis	4 6	4 4	4 0	91	96	1 700	1 900	17	17
4	Coarctation of the aorta	4 2	4 9	4 9	115	115	2 450	2 450	9	11
5	Coronary artery disease	3 6	4 7	4 3	115	115	2 500	2 700	13	14
6.	Rheumatic heart disease mit l tenosis	5 4	3 6	3 5	90	90	2 000	2 050	21	21
7	Ventricular sept l defect	2 5	7 4	7 6	90	95	9 0	1 000	20	18
8	Idiopathic myoc rdial h pertrophy	3 8	6 8	6 3	72	72	850	910	10	10
9	Normal	4 2	7 4	7 3	91	91	1 020	1 030	29	30
10.	Normal	2 8	8 6	8 7	93	86	855	790	13	13
11	Normal	3 5	7 2	7 3	75	73	835	823		12
12	Tet ology of F llot	3 5	6 9	7 0	70	75	810	860	8	9
Mean		3 8	6 1	6 0	89	90	1 360	1 400	16	15

AF Atrial fibrillation NC No change

flow decreased coronary resistance decreased heart rate and slightly increased peripheral resistance Distinct effects on myocardial contractility were not demonstrated Decreases in cardiac output and in aortic pressure were observed but were attributed to venous pooling since atrial and left ventricular end-diastolic pressures did not change It was postulated that the increased coronary flow might account for the antiarrhythmic effects of thi agent. Mierzwiak and associates[11] accumulated contradictory evidence in regard to the effects of DPH on left ventricular function Their studies showed a transient increase in left ventricular end-diastolic pressure and a decrease in maximal rate of rise in pressure (dp/dt) after 5 and 10 mg per kilogram Ventricular function curves relating left ventricular end-diastolic pressure to stroke work and stroke power showed a negative inotropic effect. Rapid injection of similar doses showed more marked negative inotropic effects including pulsus alternans and cessation of effective ventricular ejection Repeated injections produced a cumulative negative inotropic effect

The consensus of the experimental data on the cardiovascular effects of DPH seems to indicate that this agent used under experimental conditions in animals depresses myocardial function and results in peripheral vasodilatation These depressant characteristics appear to be related to the dose and to the rapidity of administration.

The present study adds further information to the above-mentioned observations on the hemodynamic effects of DPH by quantifying the effects of this agent in cardiac patients. As can be seen from Table I significant alterations were not observed in cardiac output, arterial pressure pulmonary pressures or peripheral resistance when DPH was used in doses that empirically have been noted to be clinically effective in cardiac arrhythmias (2 5 to 5 4 mg per kilogram)

The cardiovascular effects of DPH are in many ways similar to those of quinidine and procainamide These drugs are effective

dantoin

Heart rate (beats/min)		Stroke volume (cc per m)		Electrocardiogram P R		QRS		ST T	Other observations
Before	After	Before	After	Before	After	Before	After		
110	110	44	45	AF	AF	0 08	0 05	NC	
78	78	82	85	0 16	0 16	0 07	0 07	NC	Cough substernal burning
70	75	63	54	AF	AF	0 08	0 08	NC	Cough substernal burning
73	80	65	61	0 14	0 14	0 07	0 07	NC	Cough substernal burning
73	75	65	55	0 14	0 14	0 12	0 12	NC	
72	64	53	57	0 20	0 22	0 06	0 06	NC	
64	64	115	120	0 14	0 14	0 08	0 08	NC	Reduced trial premature beats
68	75	105	93	0 20	0 20	0 10	0 10	Negative T Positive T	
85	90	75	73	0 16	0 16	0 08	0 08	NC	Cough
84	92	103	95	0 20	0 20	0 06	0 06	NC	
68	83	106	88	0 16	0 16	0 08	0 08	NC	
68	68	101	95	0 18	0 18	0 10	0 10	NC	Cough
76	79	81	77						

against a variety of supraventricular and ventricular arrhythmias, but contrary to the experience with quinidine and procainamide DPH is not effective in chronic atrial flutter and fibrillation Even more important differences have been noted Quinidine and procainamide in the usual clinical doses may demonstrate anticholinergic properties which result in an increased ventricular response to a supraventricular arrhythmia.[14] On the other hand DPH in small doses has been noted to possess vagal effects which result in atrioventricular block, with a subsequent reduction in the ventricular response to a rapid supraventricular rate.[3] This pharmacologic property may result in potentiation of the vagal effects of digitalis when the two drugs are used concurrently. In addition to the effect on cardiac rhythm it is well known that quinidine and procainamide reduce cardiac output and produce hypotension.[13] These toxic effects are not unlike those seen for DPH and result from decreases in myocardial contractility and direct peripheral vasodilatation.[13] Of related interest is a recent study in which procainamide was shown to have positive inotropic effects in doses up to 10 mg per kilogram in dogs, even though there was a fall in arterial pressure that resulted from direct vasodilatation.

The selection of a pharmacologically effective yet nontoxic dose of DPH in the treatment of cardiac arrhythmias remains a point of major concern. Animal studies have consistently shown that even large doses (up to 20 mg per kilogram) are tolerated if injected slowly Smaller doses injected in less than 1 minute are often lethal Sudden death has been observed in seriously ill patients when the drug was given rapidly and this remains the limiting factor in the clinical use of this agent.[24] Respiratory arrest may precede the cessation of cardiac activity Several different therapeutic regimens have been proposed for the clinical use of DPH in cardiac arrhythmias In general it has been recommended that the initial parenteral dose

should be in the range of 5 to 10 mg per kilogram.[1] It has been our practice to administer the drug to patients in a dose of 125 to 250 mg in no less than 3 minutes. If this dose is effective then the patient is maintained on 300 to 400 mg intravenously or intramuscularly daily until oral medication can be substituted. In the absence of sufficient clinical data on dose toxicity responses we have thought that higher doses should not be utilized. Although Lang and associates[5] have evidence to show that a total dose of 15 mg per kilogram may be safely tolerated when given over several hours. In addition to cardiorespiratory toxicity it is important to remember that the standard DPH solutions are highly alkaline and result in significant local irritation at the site of injection or along the course of the vein being used for injection. In the present study the observation of marked paroxysmal coughing even with slow injection into the pulmonary artery attests further to the irritant properties of the drug.

Summary

This study records the first observations in human beings on the hemodynamic effects of diphenylhydantoin (DPH). Alterations were not noted in cardiac output peripheral resistance pulmonary pressures, or the electrocardiogram when the drug was administered in doses previously noted to be clinically effective in cardiac arrhythmias. Animal studies have shown that DPH directly reduces ventricular function and results in vasodilatation but that the cardiovascular toxicity is probably related more to the rapidity of injection than to the absolute dose. The pharmacologic actions of DPH resemble those of quinidine and procainamide with the exception that DPH has not been shown to be effective against chronic atrial flutter and fibrillation and that in small doses it may greatly augment vagal tone.

The conclusion is that in this study even though DPH did not significantly alter cardiovascular function it possesses significant toxic potential and should be administered cautiously and in doses not exceeding 10 mg per kilogram.

REFERENCES

1. Dreifus, L. S., Rabbino, M. D., and Watanabe, Y.: Newer agents in the treatment of cardiac arrhythmias, M. Clin. North America 48:371, 1964.
2. Osborne, J. A.: Diphenylhydantoin in the treatment of clinical arrhythmias, Am. J. Cardiol. 13:126, 1964.
3. Conn, R. D.: Diphenylhydantoin sodium in cardiac arrhythmias, New England J. Med. 272:277, 1965.
4. Bashour, F. A., Jones, R. E., and Edmondson, R.: Ventricular tachycardia in acute myocardial infarction. Preliminary report of the prophylactic use of Dilantin, Clin. Res. 11:397, 1963.
5. Lang, T., Bernstein, H., Barbieri, F. F., Gold, H., and Corday, E.: Digitalis toxicity. Treatment with diphenylhydantoin, Arch. Int. Med. 116:573, 1965.
6. Bernstein, H., Gold, H., Lang, T., Pappelbaum, S., Bazika, V., and Corday, E.: Sodium diphenylhydantoin in the treatment of cardiac arrhythmias, J.A.M.A. 191:695, 1965.
7. Wilcoxon, F., and Wilcox, R. A.: Some rapid approximate statistical procedures, Pearl River, N. Y., 1964, Lederle Laboratories, Publisher.
8. Harris, A. S., and Kokernot, R. H.: Effect of diphenylhydantoin sodium (Dilantin sodium) and phenobarbital sodium upon ectopic ventricular tachycardia in acute myocardial infarction, Am. J. Physiol. 163:505, 1950.
9. Mosey, L., and Tyler, M. D.: The effect of diphenylhydantoin sodium (Dilantin), procaine hydrochloride, procainamide hydrochloride, and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65, 1954.
10. Scherf, D., Blumenfeld, S., Taner, D., and Yildiz, M.: The effect of diphenylhydantoin (Dilantin) sodium on atrial flutter and fibrillation provoked by focal application of aconitine or delphinine, Am. Heart J. 60:936, 1960.
11. Lang, T., Bazika, V., Pappelbaum, S., Gold, H., Bernstein, H., Herrold, G., and Corday, E.: Autotransplanted heart-lung and cerebral venous shunt preparation. Two new techniques for pharmacologic assay of cardiovascular drugs, Am. J. Cardiol. 16:695, 1965.
12. Mixter, C. G., III, Moran, J. M., and Austen, W. G.: Cardiac and peripheral vascular effects of diphenylhydantoin sodium, Am. J. Cardiol. 17:332, 1966.
13. Gupta, D. N., Metin, M. O., Bashour, F. A., and Webb, W. R.: Effect of diphenylhydantoin (Dilantin) on coronary and systemic circulation, Clin. Res. 14:81, 1966.
14. Mierzwiak, D. S., Mitchell, J. H., and Shapiro, W.: Effect of diphenylhydantoin (Dilantin) on left ventricular function in dogs, Clin. Res. 14:12, 1966.
15. Moe, G. K., and Abildskov, J. A.: Antiarrhythmic drugs, *in* Goodman, L. S., and Gilman, A., editors: The pharmacologic basis of therapeutics, ed. 3, New York, 1965, The Macmillan Company, p. 699.

16. Conn, H. L., Jr., and Luchi, R. J.: Some cellular and metabolic considerations relating to the action of quinidine as a prototype antiarrhythmic agent, Am. J. Med. 37:685, 1964.
17. Luchi, R. J., Helwig, J., Jr., and Conn, H. L., Jr.: Quinidine toxicity and its treatment, Am. Heart J. 65:340, 1963.
18. Austen, W. G., and Moran, J. M.: Cardiac and peripheral vascular effects of lidocaine and procainamide, Am. J. Cardiol. 16:701, 1965.
19. Karliner, J. S.: Personal communication.
20. Conn, R. D.: Personal observations.

Circulatory dynamics of paired pacing in hypovolemic and cardiogenic shock

Robert H. Goetz, M.D., F.A.C.S.
Edwin M. Jallah, M.D.
Verena M. Goetz, M.D.
Bronx, N. Y.

It is easy to see that the lifesaving successes of electrical pacing of the heart in the treatment of heart block should have stimulated inquiry into the possibility of utilizing electrical stimulation of the heart in the treatment of other disorders of cardiac rhythm and of the failing heart refractory to medicinal treatment. As long ago as 1902 Woodworth[1] demonstrated that stimulation of the auricle very early in the diastole, causes an extra contraction that does not spread to the ventricle, with the result that the ventricle is missing one of the regular beats and the ventricular rate is halved. However, it was only in 1963 that Lopez, Edelist and Katz suggested that by introducing such mechanically ineffective extrasystoles the rapidly beating heart may be slowed and the patient be screened from the harmful effects of arrhythmias and tachycardias refractory to medicinal therapy. Lopez and co-workers[2] addressed themselves mainly to the effects of pacing in arrhythmias and demonstrated that the frequency of ventricular contraction could be decreased by delivering pairs of impulses, spaced in such a way that the second impulse of the pair stimulated the ventricle early in the cycle and did not lead to a discernible contraction of the ventricle. However, they paid little attention to the fact long known[illegible] that the introduction of an extrasystole into the cardiac cycle also potentiates the *force* of the following myocardial contraction. To this phenomenon the term *postextrasystolic potentiation* (PESP) has been applied. The greater the degree of prematurity of such an extrasystole, the weaker the associated ventricular pressure event and the greater the increase in the force of the postextrasystolic contraction.

Discovery of postextrasystolic potentiation has been attributed to Oskar Langendorff,[illegible] who in 1885 described the phenomenon for the heart of the frog and in 1898 confirmed it for mammalian cardiac muscle. Woodworth, working on the perfused isolated apex of the dog's heart, gave a clear description of the phenomenon when he stated that "the spontaneous beat following an extra contraction of the apex is much stronger than the regular beat" and "the more the extra contraction was has-

From the Department of Surgery, Albert Einstein College of Medicine, Bronx, N. Y.
Work supported by Grant No. H 3743 from the National Institutes of Health and the Health Research Council of the City of New York under Contract I 237.
Received for publication June 2, 1966.
Address: Department of Surgery, Albert Einstein College of Medicine, Yeshiva University, Eastchester Rd. and Morris Park Ave., Bronx, N. Y. 10461

tened the stronger was the stimulating effect." Although the earliest investigators clearly demonstrated that postextrasystolic potentiation is independent of the increase in fiber length or changes in filling of the ventricles, and therefore is a property of cardiac muscle Starling's law began to dominate contemporary thinking to such an extent that postextrasystolic potentiation became generally considered to be a part of its concept and was not pursued any further The phenomenon was rediscovered in 1941 by Catell and Gold[3] who demonstrated postextrasystolic potentiation in the cat's papillary muscle, and by Hoffman and his co-workers[4] who investigated postextrasystolic potentiation in strips of mammalian myocardium in great detail This early history of postextrasystolic potentiation has been well reviewed recently by Cranefield

If extrasystoles are introduced after every other normal cardiac cycle and in such a way that the next normal heartbeat falls into the refractory period of the extrasystole (Fig 1,B) we speak of *R-wave coupled* or *synchronous pacing* If the extrasystoles are introduced early enough in the cycle after excitability has returned but recovery of contractility has not yet taken place, effective ventricular contraction will be halved (Fig 2,B) Although this may be a desirable effect in the treatment of tachycardias, the heart rate thus produced may be too slow for optimal performance of the heart. In that case *paired pacing* can be resorted to In paired pacing pairs of stimuli (extrasystoles) are delivered in such a way that the first one drives the heart while the second one follows at termination of the absolute refractory period (Fig 1 C) The second stimulus therefore produces depolarization but is mechanically ineffective. Thus in paired pacing we gain control over the heart rate but retain the stimulating effect of postextrasystolic potentiation (Fig 2 C)

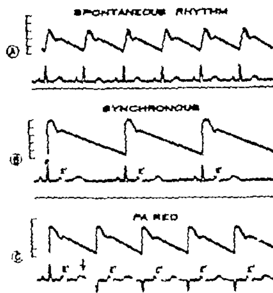


Fig 2 The effect of synchronous and paired pacing on the pulse rate. With synchronous pacing the pulse rate is half that of the spontaneous rhythm. In paired pacing pulse rate can be controlled by speeding up the rate of impulses. *R*, R wave of normal sinus rhythm. *E*, Effective extrasystole. *E'* Mechanically ineffective extrasystole.

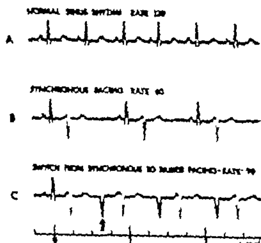


Fig 1 The electrocardiogram in synchronous (R-coupled) pacing (*B*) and paired pacing (*C*). At the arrow in C, switch from synchronous to paired pacing. For explanation see text.

The present study was undertaken to investigate the effects of postextrasystolic potentiation on the failing heart in hypovolemic and cardiogenic shock A brief summary of this material was presented elsewhere.

Methods

Experiments were carried out in 30 unselected adult mongrel dogs weighing 10 to 25 kilograms, anesthetized with 30 mg per kilogram of sodium thiopental. In 10

animals (Group 1) the chest was opened through the fifth left intercostal space and ventilation was maintained with a Bird respirator using 100 per cent oxygen. The animals were heparinized with 1 mg of heparin per kilogram of body weight. Cardiogenic shock was produced by partial occlusion of the pulmonary artery and the intravenous administration of 100 mg of Nethalide a beta adrenergic blocking agent. All animals developed ventricular fibrillation after which the occlusion of the pulmonary artery was released and the heart defibrillated. In 10 dogs (Group 2) the heart was made to fail by producing irreversible hemorrhagic shock according to the method of Wiggers and Fine. The animals were bled from the femoral artery into a graduated reservoir that was adjusted so that the blood pressure of the animals could be kept at a mean pressure of 60 and 30 mm Hg for 30 and 45 minutes, respectively, or until they spontaneously started to take up blood.

The ECG was monitored using the conventional limb leads, and the systemic pressure was recorded with P23d Statham transducers after cannulation of the femoral artery in all animals. Ventricular pressures were recorded through a lumen provided in the electrode catheter (Group 2) or through catheters placed directly into the ventricles at the time of thoracotomy (Group 1). The maximum rate of ascent of ventricular pressure (maximum dp/dt) was computed with a linear R-C differentiating circuit and measured directly as the tangent to the rise in pressure at the point of the maximum differentiated pressure. Cardiac output and stroke volume were calculated from dye-dilution curves. Indocyanine (Cardio-Green) was injected into the inferior vena cava and blood was collected at a constant flow rate from the femoral artery by means of a withdrawal infusion pump. Stroke work (in gram-meters) was then calculated as a product of stroke volume (in milliliters) and mean ejection pressure and stroke power (in gram-meters per second) by dividing stroke work by the duration of ejection. Mean ventricular ejection rate (in milliliters per second) was calculated by dividing stroke volume by the duration of the ejection. The tension-time index (TTI) per beat (in millimeters of mercury per second) was calculated in some animals as the product of the mean systolic pressure and the duration of ejection. In order to compare values obtained in different animals the data were expressed as per cent of control measurement and an effort was made to pace the heart at the rate of the intrinsic sinus rhythm.

The heart was paced at 3 to 5 milliamperes by a transistorized battery-driven pulse generator capable of delivering either single or paired electrical stimuli.* In later experiments, the R wave coupled pacemaker was employed. The depolarizing impulses had a width of about 2 milliseconds. Animals in hemorrhagic shock (Group 2) were paced by means of an intravenous bipolar electrode inserted into the right ventricle via the femoral or external jugular vein. In the animals of Group 1 electrodes were implanted directly into the subendocardial layer of the myocardium of either the right or left ventricles in pairs or as a single electrode with an independent electrode attached to the chest wall. At the end of the experiment an autopsy was performed to determine the position of the catheters and electrodes.

Attempts to capture the fast beating heart of the dog by paired pacing caused ventricular fibrillation in a large number of animals even when the stimulation was at a rate higher than that of the intrinsic sinus rhythm. This difficulty was overcome by employing R wave coupled pacing first and then switching from coupled to paired pacing to gain control over the heart rate as indicated in Fig. 1C. At the time of switching from coupled to paired pacing the instrument maintained phase lock between the extrasystole and the preceding cardiac cycle. Since we have followed this routine we have no longer seen fibrillation.

Results

The normal heart. The effects of pacing the normal heart at its original rate by paired stimuli are not very striking. Although one may get an increase in peak systolic ventricular pressure and a slight drop in ventricular end-diastolic pressure the most constant evidence of paired pacing

*Medtronics, Inc., Minneapolis, Minn.

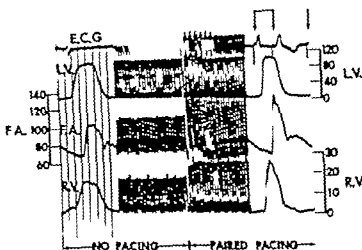


Fig. 3. The effect of paired pacing on entricular and systemic blood pressures. Note the marked increase in peak systolic pressure and at of ascent of entricular pressure. Slight decrease in entricular end-diastolic pressures. Note that the heart as paced at pproximately the same as normal rate.

is a slight shortening of the duration of ventricular ejection and an increase in the maximum rate of ascent of ventricular pressure (max. dp/dt). These findings are well illustrated in Fig. 3 for both the left and the right ventricles. Close study of the pressure tracings during pai ed pacing re veals changes in the individual ventricular peak pressures which are related to the P wave n the ECG i.e. the atrial systole. Whenever atrial contractions coincide with ventricular diastole i.e. when the atrium contributes to the filling of the ventricle peak systolic pressures are higher.

In the normal heart cardiac output and stroke volume were not altered in a con tant pattern by paired pacing. A tend ency toward diminished cardiac output was apparent n many experiments, which can be explained by the interference with the physiologic synchronization of atrial and ventricular contractions. The increase in th maximum rate of ascent of ventricular pressure resulted in an increase in stroke work which in view of the lack of changes n stroke volume is, however of no benefit to the organism as a whole.

P ed pacing n th a utely fail ng heart. It is n the fa ling heart that postextra systolic potentiation produces its most striking effect on the ci culatory dynamics. Ventricular function had been severely compromised in all of our animals. In one group of animals the right ventricle had been subjected to gross dilatation by obstruction of the outflow tract resulting in ventricular failure and fibrillation which in many animals required repeated counter shocks before paired pacing could be started. Similarly the heart had greatly deteriorated in animals sul jected to hemorrhagic shock, with marked elevation of ventricular end-diastolic pressures before initiation of paired pacing. The exper mental model in many of our animals simu lated closely the clinical situation seen in patients.

Although marked improvement in left ventricular performance was observed n both types of failure our data ndicate that greater benefit was derived n animals in which failure was nduced by constric tion of the pulmonary artery than n those suffering from hypovolem shock.

In the animals w th a f l ng heart (Fig 4) paired pacing consistently ncreased the mean systemic and left nd right vent icu lar peak pressu es. A decr ase n ventricular end-diastolic pressu e was eg stered n all animals. Ventricular jection time was only sl ghtly shortened. Fig. 5 was ol tained f om an nimal in ardiogenic shock in which the heart could not even ma nta n a system c blood pressure of 30 mm Hg and n which the heart had al eady been e suscitated. On paired pacing left ventricu

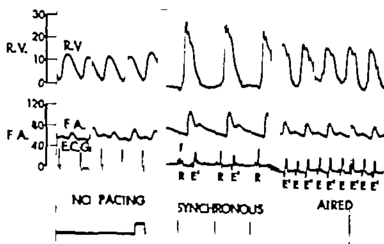


Fig. 4. The effect of synchronous and paired pacing on right ventricular (R.V.) and systemic pressures (F.A.) in cardiogenic shock. Rate of effective ventricular contractions is roughly the same during pacing as during the control period. E'. Ineffective extrasystole. E. Effective extrasystole driving the ventricle. R. Normal R wave.

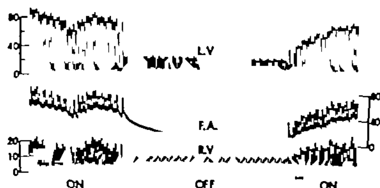


Fig. 5. The effect of paired pacing in an animal in severe cardiogenic shock after occlusion of the pulmonary artery. The heart is paced at the same rate recorded during spontaneous activity.

lar pressure reached 80 mm. Hg, right ventricular pressure 20 mm. Hg, and the systemic blood pressure could be sustained during pacing at 80/50 mm. Hg. These pressures were maintained as long as pacing was continued but immediately dropped to shock levels when pacing was stopped.

Fig. 6 demonstrates the effect of paired pacing on a heart failing in severe irreversible hemorrhagic shock. As can be seen, the heart rate had dropped to 40 and the ventricles were unable to generate any pressure. The administration of a vasoconstrictor and pacing by conventional single impulses could not resuscitate the heart. Paired pacing produced marked improvement in all recorded parameters, and the animal responded to the administration of vasoconstrictors.

The data for 16 experiments have been summarized in Figs. 7 and 8 for the systemic and ventricular systolic peak pressures and the ventricular end-diastolic pressures. For comparison, the changes have been expressed in per cent of the pressures recorded before paired pacing. As can be seen, systemic diastolic pressures did not increase as much as or as consistently as did systolic peak pressures (Fig. 7). The rise in ventricular systolic peak pressures, together with the fall in ventricular end-diastolic pressures, indicate the bene-

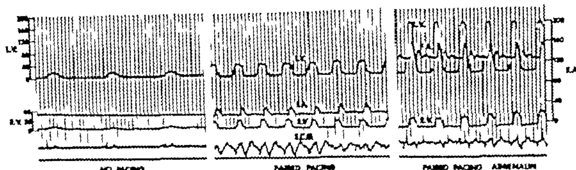


Fig. 6. The effect of paired pacing on systemic (*R.A.*) and ventricular (*L.V.* and *R.V.*) pressures in an animal in severe irreversible hemorrhagic shock. Systemic blood pressure could not be raised above 40 mm. Hg by paired pacing. The addition of epinephrine drip raised the pressure to normal values.

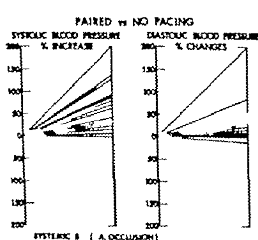


Fig. 7. Changes in systolic and diastolic blood pressures with paired pacing in 16 animals with failing hearts after occlusion of the pulmonary artery. The changes are expressed in per cent of control values recorded immediately before pacing.

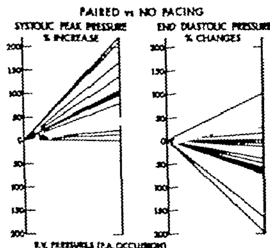


Fig. 8. Changes in right ventricular peak systolic pressure and ventricular end-diastolic pressure with paired pacing. Changes expressed as per cent of control values immediately before pacing. Failing heart after occlusion of the pulmonary artery.

ficial hemodynamic effects on the failing heart (Fig. 8). In one animal right ventricular end-diastolic pressure did for unknown reasons appreciably rise.

By far the most striking effect of paired pacing concerns the changes in the maximum rate of ascent of ventricular pressure (Fig. 9). These changes reflect much more accurately the marked increase in stroke power and in the contractile state of the myocardium which results from paired pacing than do the changes in the ventricular pressure.

Cardiac output and stroke volume during paired pacing. In the normal heart cardiac output and stroke volume did not improve on paired pacing despite the fact that the duration of the systolic ejection was slightly decreased and the ascent of ventricular pressure and the peak systolic pressure were increased.

In the failing heart, the stroke volume was increased in 13 of 15 animals investigated whether failure was caused by occlusion of the pulmonary artery or hemorrhagic shock (Figs. 10 and 11). However the greater changes were seen in the animals in cardiogenic shock after occlusion of the pulmonary artery. The increases in stroke volume varied between 16 and 175

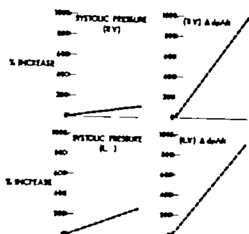


Fig 9 Comparison of changes in ventricular peak systolic pressures and rate of ascent of ventricular pressure (dp/dt) during paired pacing. The changes are expressed as per cent of control values obtained immediately before pacing. Failing heart after occlusion of the pulmonary artery.

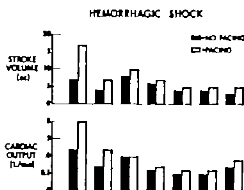


Fig 10 Stroke volume and cardiac output in 7 animals before and during paired pacing of heart in hemorrhagic shock.

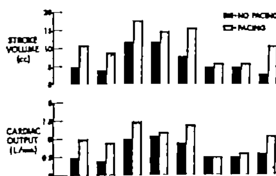


Fig 11 Stroke volume and cardiac output in 8 animals before and during paired pacing of the failing heart after occlusion of the pulmonary artery and defibrillation.

per cent with an average of 55 per cent for the hemorrhagic group and between 20 and 260 per cent with an average of 72 per cent for the cardiogenic shock group. Using these values for stroke volume we could calculate stroke work stroke power and mean ventricular ejection rate. All of these parameters were markedly increased on paired pacing in all of our experiments, as set forth in Table I. It should be mentioned that the changes were also obtained in those hearts which had been subjected to a blockade of the sympathetic nervous system by the administration of a beta adrenergic blocking agent.

Implanted versus intracavitary electrodes. The effects of paired pacing were not dependent on the types of electrodes employed. Electrodes were routinely implanted in the myocardium in those animals which underwent thoracotomy for occlusion of the pulmonary artery. Intracavitary bipolar electrodes of our own design were employed in the animals subjected to hemorrhagic shock. However in some animals of both groups both types of electrodes were employed affording a comparison of cardiac dynamics when either type of electrodes was used. Only slight differences were encountered when either the right or left ventricle was paced (Fig 12) or when both electrodes were implanted into the myocardial wall of the heart rather than implanting only one into the myocardium and employing the other as an independent electrode attached to the chest wall. However in the latter case slightly higher driving forces were required.

Discussion

Paired pacing takes advantage of the fact that recovery of electrical excitability of the heart precedes recovery of contractile activity. It is thus possible to introduce an electrical impulse immediately after termination of the absolute refractory period which induces depolarization of the cardiac muscle but does not produce an effective mechanical response. Thus, *if two* successive electrical stimuli are appropriately paired only the first results in a cardiac contraction. At the same time the strength of the beat that follows the pair, i.e. the postextrasystolic ventricular contraction is greatly increased. This postextrasystolic *potentiation* (PESP) should

Table I. Cardiovascular hemodynamics before and during paired pacing

Experiment number	Rhythm and rate	Pressure (mm. Hg)	Cardiac output (ml./min.)	Stroke volume (ml.)	Max. dp/dt (mm. Hg/sec.)	Stroke work (Gm. M.)	Mean ventricular ejection rate (ml./sec.)	Stroke power (Gm. M./sec.)
851/6	SR 110	28/2	474	4 3	280	0 8	30 7	5 7
	PP 98	72/0	897	9 2	1200	4 8	65 7	34 3
851/0	SR 103	6/0	430	4 1	56	0 18	22 8	1 0
	PP 99	18/—2	944	9 5	289	1 37	59 4	8 6
853/14	SR 38	8/5	Unm.	Unm.	Unm.	—	—	—
	PP 93	18/7	416	4 5	400	0 52	34 6	4 0
855/4	SR 120	10/2	520	4 3	80	0 25	30 7	1 8
	PP 95	22/2	510	5 4	332	0 78	35 6	5 6
860/3	SR 125	13/2	530	4 2	192	0 33	35 0	8
	PP 120	19/2	611	5 3	580	0 88	54 0	8 8
864/3	SR 125	14/1	700	5 6	200	0 40	40 0	2 9
	PP 103	29/1	810	7 9	735	1 59	65 8	13 3
861/3	SR 100	11/2	500	5 0	100	0 32	35 7	2 4
	PP 94	17/0	500	5 3	200	0 65	44 2	5 4
863/1	SR 120	22/9	630	5 3	124	0 486	37 9	3 5
	PP 100	25/0	670	6 7	175	1 205	55 8	10 0
866/1	SR 180	16/5	600	3 3	116	0 260	33 0	2 6
	PP 126	30/5	1 100	8 7	520	1 566	87 0	15 7
Mean values	SR 114	14/3	548	4 5	144	0 38	33	2 8
	PP 103	28/1	721	6 9	492	1 48	56 0	11 7

SR, Spontaneous rhythm before pacing. PP, Paired pacing. Unm., Data could not be recorded.

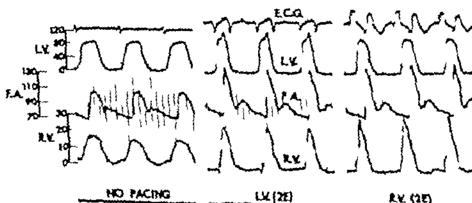


Fig. 12. The effect of pacing was essentially the same whether the right or the left ventricles were paced and whether two electrodes (2E) were applied to the ventricular wall or one of the electrodes was applied to the chest as an independent electrode.

not be confused with the well known phenomenon of *augmentation* which depends on the end-diastolic volume of the ventricle and the filling time according to the Frank-Starling law. PESP is not like augmentation dependent on the integrity of the ventricular chamber and has been demonstrated to occur in strips of mammalian myocardial muscle. Thus postextrasystolic potentiation may be seen when the rate of effective ventricular contraction during paired pacing is the same as the spontaneous heart rate. However both augmentation and potentiation may coexist and

the benefit from both is responsible for the marked changes in pressure seen on R wave coupled pacing.

The effect of paired pacing on the pressure pattern relates strictly to the degree of prematurity of the extrasystolic depolarization. Rate, voltage, and the interval between the paired pulses are critical, and if not properly adjusted paired pacing may be detrimental rather than beneficial in its effect. If the extrasystole is placed immediately after the absolute refractory phase of the driving pulse, it will not cause any change in the ventricular pressure tracing.

Our investigations show that whereas paired pacing improved ventricular functions in the failing heart, it interfered with the physiologic regulating mechanism in the normal heart. The increase in the force of ventricular contraction, the increase in the peak systolic pressures, and the increase in the rate of ascent of the ventricular pressure are not paralleled by an improvement in cardiac output or stroke volume in the normal heart. In contrast, the heart made to fail by hypovolemic hypotension or obstruction of the ventricular outflow tract responded regularly with an increased stroke volume and cardiac output. The most remarkable results were obtained in hearts unable to maintain adequate perfusion pressure and unresponsive to vasoconstrictor drugs.

Although the improvements in the peak systolic pressures were impressive enough, the changes occurring in the rate of ascent *of ventricular pressure and the velocity of* contraction were more remarkable. As Sonnenblick[7] has pointed out, the force-velocity relationship is the most fundamental mechanical property of the contractile portion of the muscle during activity. On the basis of our data, the conclusion can be made that postextrasystolic potentiation is characterized by an alteration in the velocity-dependent aspects of myocardial contraction. Hence postextrasystolic potentiation has all of the characteristics of a true inotropic effect, with a decrease in ventricular diastolic pressures and an increase in ventricular contraction.

Although paired pacing may prove to be a practical method of improving cardiac contraction in hearts failing for reasons *other than coronary artery disease,* it may be disappointing in such patients whose coronary blood flow cannot expand in response to increased requirements, since paired pacing is associated with an increase in oxygen requirements. As Katz[11] has pointed out, the hazards associated with paired ventricular responses unaccompanied by significant slowing of the total ventricular responses may well outweigh the benefits to be derived from augmentation and potentiation in a seriously diseased heart.

The role played by extrasystolic potentiation in producing the changes in blood pressure seen with spontaneous changes in rhythm is not yet clear. Although the irregular heights of the pressure pulses in atrial fibrillation are generally attributed to variations in the end-diastolic fiber length according to the Frank-Starling law, Hoffman and co-workers are of the opinion that random spontaneous premature beats may, at times, induce postextrasystolic potentiation. They admit, however, that atrial premature beats do not, as a rule, reach the ventricle early enough to cause marked potentiation. Similarly, the fact that patients may be clinically improved when they are digitalized to toxic levels and show sustained bigeminy has been difficult to understand and could be due to postextrasystolic potentiation.

Although the mechanism of postextrasystolic potentiation remains unexplained, all investigators agree that its clinical potential in achieving almost instantaneously by electrical impulses what is difficult to *attain by pharmacological and other means* deserves serious consideration. Our studies would indicate that besides the area of disturbances in rhythm, the clinical application of extrasystolic potentiation may be in the area of low cardiac output failure, as in cases of irreversible shock or in patients after cardiac surgery who are unable to maintain an effective blood pressure due to ineffective ventricular contractions and who are unresponsive to sympathicomimetic drugs.

Ventricular fibrillation has proved to be the main hazard of paired pacing *in our* study, and many animals were lost. By employing R wave coupled pacing first and then switching over to paired pacing, we eliminated this complication. Since this method of capturing the heart has been

employed ventricular fibrillation has no longer been experienced

Summary and conclusion

The effect of paired pacing on the circulatory dynamics was studied in normal hearts and in hearts made to fail by hypovolemic hypotension and obstruction of the ventricular outflow tract. In the normal heart paired pacing by virtue of the resultant postextrasystolic potentiation increased peak systolic pressures and the maximum rate of ascent of ventricular pressure (max. dp/dt) but cardiac output remained essentially unaffected

In contrast, the failing heart responded regularly with an increase in stroke volume and systolic peak pressure However this effect was overshadowed by the greater increase in the maximum rate of ascent of ventricular pressure. Consequently stroke work mean ventricular ejection rate and stroke power increased considerably

The resuscitative powers of paired pacing were most striking in hearts which were unable to maintain any systemic pressure so long as the muscle would respond to stimulation Our data suggest that postextrasystolic potentiation is characterized by an alteration in the velocity-dependent aspect of myocardial contraction and has all the characteristics of a true inotropic effect

Postextrasystolic potentiation must not be confused with augmentation which is dependent on the fiber lengths and the length of diastole according to the Frank Starling law Postextrasystolic potentiation therefore may be seen in hearts which are effectively paced at the same rate as the spontaneous rate prior to pacing

The clinical application of extrasystolic potentiation may be in the area of low cardiac output failure in hearts that are not afflicted with coronary obstruction.

Ventricular fibrillation remains the main hazard of paired pacing By employing R wave coupled pacing first and then switching to paired pacing subsequently we eliminated this complication

REFERENCES

1 Braunwald, E. Ross, J. J. Sonnenblick, E. H. Frommer, P. L. Braunwald, N. S. and Morrow, A. G. Slowing of heart at electroaugmentation of ventricular performance and increase of myocardial oxygen consumption produced by paired electrical stimulation. Bull. New York Acad. Med. 11:481 1965

2. Catell, M and Gold, H. The relation of rhythm to the force of contraction of mammalian cardiac muscle Am. J. Physiol 133:236, 1941

3 Chardack, W. M. Gage, A. A. and Dean, D. C. Paired and coupled electrical stimulation of the heart, Bull. New York Acad. Med 41:462, 1965.

4 Cranefield, P. F. The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contraction. A historical review Bull. New York Acad. Med 41:419 1965.

5 Cranefield, P. F. Scherlag, B. J. Yeh, B. K. and Hoffman, B. F. Treatment of acute cardiac failure by maintained postextrasystolic potentiation Bull. New York Acad. Med 10:903 1964

6. DeBoer, S. Halbierung des Ventrikelrhythmus durch Induktionsschläge Zentralbl. Physiol 30:503, 1915

7 Frey, J. O. J. Hemodynamic alterations in left ventricular function consequent to ventricular pacing, Am. J. Physiol 208:275 1965

8 Goetz, R. H. Bipolar catheter electrode as temporary pacemaker in Stokes-Adams syndrome, Surg. Gynec. & Obst. 116 712, 1963

9 Hoffman, B. F. Bindler, E. and Suckling, E. E. Postextrasystolic potentiation of contraction in cardiac muscle Am. J. Physiol. 185:95 1956

10 Hoffman, B. F. Bartelstone, H. J. Scherlag, B. J. and Cranefield, P. F. Effects of postextrasystolic potentiation on normal and failing heart, Bull. New York Acad. Med 41:498 1965

11 J. Bab, E. M. Goetz, R. H. and Goetz, V. M. Comparison of dynamic responses to single and paired pacing in the failing heart in shock Surg. Forum 16:1 1965

12 Katz, L. N. Effects of artificially induced paired and coupled beats Bull. New York Acad. Med. 11:478, 1965

13 Langendorff, O. Über elektrische Reizung des Herzens Arch. Physiol. Arch. Anat. Physiol. Physiol. Abt. Suppl. p. 284 1885

14 Langendorff, O. Untersuchungen am überlebenden Säugetierherzen III Abhandlung Vorübergehende Unregelmässigkeiten des Herzschlages und ihr Ausgleichung Pflüger Arch. ges. Physiol 70 473 1898

15 Lopez, J. F. and Perkov, S. N. J. Effect of paired electric stimulation in acute right ventricular failure in dogs B. B. New York Acad. Med 41 546, 1965

16 Siebens, A. A. Hoffman, B. F. Cranefield, P. F. and Brooks, C. McC. Regulation of contractile force during ventricular arrhythmias Am. J. Physiol 197:971 1959

17 Sonnenblick, E. H. Force velocity relations in mammalian heart muscle Am. J. Physiol 202:931 1962

18 Woodworth, R. S. Maximal contraction, staircase contraction, refractory period, and compensatory pause of the heart, Am. J. Physiol. 8:213 1903 1903

19 Woodworth, R. S. p. 35

The effects of potassium on the positive inotropic action of ouabain

Keith Cohn, M.D.
*Suellen Pirages**
Donald C. Harrison, M.D.
Palo Alto, Calif.

The complex interactions between potassium and digitalis glycosides have been studied for many years.

Although it has been well established that toxic doses of digitalis cause a loss of cardiac potassium,[1,2] the influence of therapeutic doses of this drug on changes in myocardial potassium is less predictable. Several studies have shown that therapeutic doses of digitalis may result in a loss of cellular potassium,[8] chiefly by decreasing the influx of potassium.[13] Other investigators, however, have observed that digitalis may increase contractility in the absence of a loss of potassium[2,4-6,11,16] and that depletion of myocardial potassium may also result from drugs which have a negative inotropic effect.[14-17] Thus, it appears to be unlikely that shifts in cellular potassium primarily account for the digitalis-induced augmentation of contractility.[1]

The ability of potassium to antagonize cardiac arrhythmias produced by digitalis has been repeatedly confirmed,[8-2] and it has been demonstrated more recently that depletion of total body potassium may enhance the development of digitalis toxicity.[22] Furthermore, increased concentrations of extracellular potassium have been reported to inhibit the action of cardiac glycosides on the duck embryo,[2] to abolish the loss of cellular potassium produced by digitalis,[23,24] and to prevent myocardial contracture resulting from toxic amounts of this drug.[8,27] On the other hand, several reports suggest that changes in extracellular potassium do not significantly affect the inotropic action of digitalis glycosides.[28-31]

Because of the discrepant observations that potassium clearly influences several actions of glycosides without also affecting the digitalis-produced increase in cardiac contractility, it seemed to be appropriate to reinvestigate the influence of varying concentrations of extracellular potassium on the action of ouabain, employing an isolated muscle preparation.

Methods

Nineteen studies were carried out on right ventricular strips from male guinea pigs weighing 300 to [illegible]00 grams which

From the Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif.
Supported by National Institutes of Health Grant HE [illegible] and General Research Grant FR [illegible].
Received for publication June 7, 1966.
*Fellow in Cardiology, Stanford University School of Medicine and Palo Alto–Stanford Hospital.
**Research Technician.
***Assistant Professor of Medicine, Stanford University School of Medicine.
Requests for reprints should be addressed to: Dr. Donald C. Harrison, Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif. 94304.

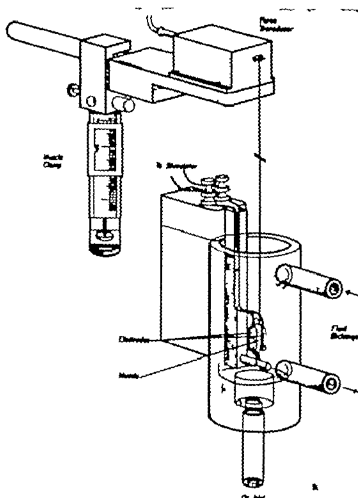


Fig. 1. Diagram of apparatus.

were sacrificed by a sharp blow to the head. Their hearts were removed and right ventricular strips measuring approximately 1 sq. mm. by 8 to 10 mm. were prepared. These strips were mounted in a muscle chamber (Fig. 1) containing 50 ml. of an electrolyte and glucose solution modified from the solution of Feigen and associates[12] to contain 2 mEq. per liter of magnesium. The bath was maintained at 37°C and 99 per cent O and 1 per cent CO were continuously bubbled through, resulting in a bath pH of 7.4. The muscle strips were stimulated with a Grass S-4 stimulator at voltages of at least 50 per cent above threshold with a duration of msec. and a frequency of 1 per second. The stimulus was delivered through platinum electrodes measuring 3 by 10 mm. mounted on either side of the muscle strip (Fig. 1).

The isometric tensions were measured with a Statham G7B-3-350 isometric force transducer and were recorded on a direct writing Grass Model 5 multichannel oscillograph. The first derivative of the isometric tension (dF/dt) was recorded continuously with an R-C differentiating circuit.[13] Initially the muscle strips were stretched to obtain maximal developed tension (averaging approximately 35 per cent greater than initial length) and then studied at a length producing slightly submaximal tensions. After each muscle was prepared it was allowed to stabilize for at least 1 hour. Tension and peak dF/dt will remain constant for a period of 4 hours under these conditions.

The isometric tension and first deriva

tive of this tension (dF dt) was determined for each muscle strip at concentration of potassium f 2 5 and 10 mEq per liter in the bath After the observations were made at ? mEq per liter a standard solution of potassium chloride containing 50 mEq per liter was added to give bath concentrations of 5 nd 10 mEq per liter Each muscle was all wed to rem in at a given level of pota sium f r 15 minutes before study The solution wa then removed from the bath and repla ed with one containing ? mEq per l ter potassium No preparation was stud d unless the tension returned to the origin l base-line value for mEq per liter potassium Ouabain was then added to produce a bath concentr ation of 25 μg per 100 ml and at least 1 hour wa allowed for the development and tabilization of the increased tension and r te of development of tension Potassium chloride wa again added to produce a bath con entration of 5 and 10 mEq per liter and all mea urements were repeated fter 15-minute periods of stabilization The concentration of potassium in the bath was determined by means of standard spectrophotometry both before and after the addition of ouabain Statistical analysis was performed employing the t test for paired samples.

Results

A The effect of ch nges in concentration of potassium The isometric tension at 2 mEq per liter potassium was significantly greater than that recorded at the normal 5 mEq per liter ($p < .001$) (Table I Figs. 2 and 4) There was no significant difference between the tension developed at 5 and 10 mEq per liter (Figs. 2 and 4) The changes in the peak first derivative of tension (dF dt) closely paralleled those for developed tension (Table I Figs. 3 and 5)

B The effects of varying concentrations of potassium on the inotropic action of ouabain At all concentrations of potassium ouabain produced a significant increase in tension and rate of development of tension (dF/dt) ($p < .001$) (Table I Figs. 2 and 3) The magnitude and per cent increment in tension and dF dt produced by ouabain at 2 mEq per liter potassium was not significantly different from that produced at 5 mEq per liter However the maximal attained tension and peak dF/dt were significantly greater at 2 than at 5 mEq per liter since the initial base line tension at ? mEq per

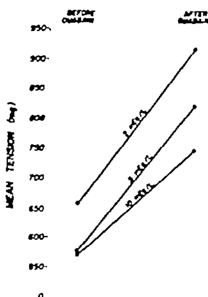


Fig. 2 Shown is the mean developed tension in milligrams at concentrations of extracellular potassium of 2 5 and 10 mEq per liter before and after the addition of ouabain to the bath.

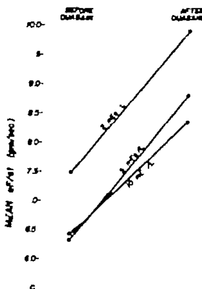


Fig. 3 Shown is the mean peak dF/dt, in grams per second at concentrations of extracellular potassium of 2 5 and 10 mEq per liter before and after the addition of ouabain to the bath.

Table 1 *Force and dF/dt at varying concentrations of extracellular K*

Study	K (mEq per liter)					
	2		5		10	
	F	*dF/dt*	*F*	*dF/dt*	*F*	*dF/dt*
1 B	53	7 04	40	5 36	36	5 44
A	93	11 35	80	11 10	70	10 70
2 B	96	12 45	75	9 55	84	10 30
A	1 38	15 45	1 16	14 72	1 07	13 50
3. B	75	8 09	66	6 78	65	6 70
A	1 28	11 35	1 16	10 40	1 05	9 45
4 B	85	9 65	77	8 30	68	7 63
A	1 10	11 65	1 06	11 00	1 04	10 90
5 B	63	6 45	73	6 45	69	6 80
A	90	8 28	86	7 90	85	8 75
6 B	45	4 54	39	4 09	42	4 28
A	75	6 42	65	6 16	57	5 28
7 B	86	8 05	73	6 80	78	7 50
A	1 21	12 10	1 13	11 10	1 03	10 70
8. B	45	5 35	36	4 41	36	4 52
A	50	6 33	43	4 95	38	4 58
9 B	48	4 91	41	3 80	41	3 95
A	63	6 07	53	5 10	46	4 32
10 B	99	10 00	96	10 15	1 00	11 01
A	1 30	15 85	1 40	13 60	1 34	13 55
11 B	50	5 61	44	4 95	45	4 83
A	72	8 15	60	6 95	54	6 85
12. B	51	6 25	46	5 62	45	5 45
A	66	8 70	56	6 66	49	5 61
13. B	39	6 45	52	5 52	47	5 68
A	70	8 35	65	7 75	60	6 99
14 B			58	6 88	56	6 38
A			77	8 88	67	7 74
15 B			50	5 48	47	5 48
A			76	8 25	69	8 01
16. B			47	5 15	45	4 85
A			82	9 30	80	8 75
17 B	46	6 60	41	5 44	42	5 65
A	59	7 63	56	7 14	50	6 63
18 B	66	9 05	6[illegible]	8 10	62	7 50
A	74	9 22	60	7 46	59	7 18
19 B	86	9 20	76	7 90	77	8 05
A	1 05	11 30	94	9 50	82	8 85
Mean B	64	7 47	57	6 33	57	6 42
A	91	9 91	82	8 83	74	8 33

F Force, in grams; *dF/dt* First derivative of force in grams per second; *B* Before ouabain; *A* After ouabain.

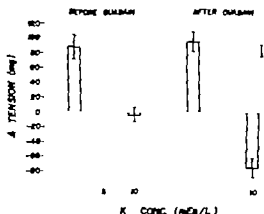


Fig. 4. Δ tension indicates the mean difference between the tension developed at the normal concentration of extracellular potassium (5 mEq. per liter) and the tension recorded at either 2 or 10 mEq. per liter potassium. Measurements were made before and after the addition of ouabain to the bathing solution.

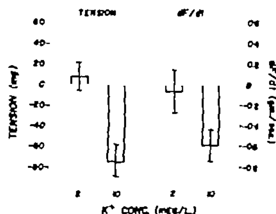


Fig. 6. The magnitude increase in tension and peak dF/dt produced by ouabain are expressed as the differences between the increase developed at the normal concentration of potassium (5 mEq. per liter) and the increment produced by ouabain at either 2 or 10 mEq. per liter potassium.

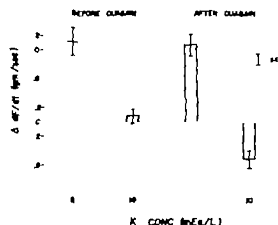


Fig. 5. Demonstrates the change in dF/dt expressed as the difference between the peak dF/dt recorded at 5 mEq. per liter potassium and the dF/dt produced when the concentration of potassium in the bath was changed to 2 or 10 mEq. per liter.

liter was also greater ($p < .001$) (Table I, Figs. 2-6).

At a concentration of potassium of 10 mEq. per liter the increment in tension and peak dF/dt produced by ouabain was significantly less than at 5 mEq. per liter and the attained tension at 10 mEq. per liter was also significantly smaller ($p < .001$) (Table I, Figs. 2-6).

Concentrations of potassium in the bath were found to vary by no more than ±0.1 mEq. per liter after the addition of ouabain. In all instances the direction and magnitude of changes in dF/dt closely approximated those of developed tension.

Discussion

These studies clearly demonstrate that the isometric tension and dF/dt in ventricular muscle strips may be altered by a change in the concentration of extracellular potassium. At low concentrations the development of tension is greater than at normal or high levels of extracellular potassium. This observation is in agreement with other reports.[23,33,34] Hajdu[17] offered an explanation for these findings by suggesting that contractile force is affected by the ratio of intracellular monovalent cation content to actomyosin. Thus, with a low concentration of extracellular potassium net efflux of cellular potassium is increased and an increase in contractile force will result.

In the present studies high levels of extracellular potassium did not reduce isometric tension or maximum dF/dt. These findings are in agreement with those of Green and associates,[34] Leonard and Hajdu[35] and Garb and Venturi[33] who found no decrease in contractile force with moderate increases in concentrations. Above levels of 10 mEq. per liter potassium negative inotropic effects have been observed.[34,35] The observations that small

changes in potassium can affect the association and dissociation of actomyosin[46] may partly explain the effects of this ion on myocardial contractility. Leonard and Hajdu[14] believe that changes in contractile force produced by variations in concentrations of cation are not due to changes in resting membrane potential.

Ouabain produced significant increases in isometric tension and peak dF/dt in normal muscle strips, confirming the findings of previous investigators that digitalis glycosides exert a positive inotropic action on nonfailing myocardium.[4-49]

At low and normal concentrations of extracellular potassium the increase in isometric tension and peak dF/dt produced by ouabain were of the same magnitude (Figs. 2, 3, and 6). The maximal tension attained at 2 mEq. per liter potassium was greater than at 5 mEq. per liter since the low levels of potassium had already produced a positive inotropic effect, with resultant higher base-line tensions. Thus, the positive inotropic effect of a low level of extracellular potassium and of ouabain are additive. High concentrations of extracellular potassium significantly impaired but did not abolish the positive inotropic action of ouabain (Figs. 2-6).

These studies are contrary to the generally accepted findings which have suggested that changes in potassium have no effect on the inotropic action of digitalis. Garb and Venturi[23] noted that concentrations of potassium between 3.5 and 8.5 mEq. per liter did not alter the inotropic effects of ouabain. These studies, however, were carried out in failing cat papillary muscles, a notably unstable preparation. Leonard and Hajdu[25] found no change in the inotropic action of digitalis at varying concentrations of potassium, but they studied only ranges from 4.7 to 7.5 mEq. per liter potassium. Leight and associates[26] have made similar observations in intact animals, but such factors as cardiac rate, afterload, and cardiac output were not controlled.

Williams and associates[27] reported that the suppression of ouabain-induced arrhythmias by KCl did not abolish the positive inotropic effect of the glycoside and, in fact, permitted the administration of additional amounts of the glycoside which produced a further increase in contractile force. The relative magnitudes of the ouabain-induced increase in contractility at different concentrations of extracellular potassium were not compared, however, so that this study neither confirms nor contradicts the present report.

The findings of Lee and associates are in partial agreement with ours in that those authors noted that the inotropic effects of ouabain were diminished and delayed in the presence of high levels of extracellular potassium. In a potassium-free medium, however, the ouabain-induced augmentation of contractility was completely abolished and contracture developed. Burstein and associates[44] also reported that infusion of KCl reversed the beneficial effects of lanatoside-C on the failing heart in a heart-lung preparation.

Studies by Nayler[45] in isolated toad hearts demonstrated that normal concentrations of potassium in the perfusing solution (3.2 mM. per liter) resulted in a maximal inotropic response to G-strophanthin. At lower levels of concentrations of external K, the inotropic effect appeared after a shorter delay but was reduced in magnitude and duration. At a concentration of potassium of 4.8 mM. per liter no inotropic response was recorded. Interpretation of this data is difficult, however, since measurements of arterial pressure were employed as the index of inotropic effect.

Since the precise mechanism of action of digitalis remains in question, it seems to be impossible to explain definitively the combined effects of potassium and the glycosides on the contractility of cardiac muscle. Increases in extracellular potassium does antagonize the retardation of the flux of potassium induced by digitalis.[30,31] Page[46] believes that the glycosides and potassium compete for a critical site involved in the active transport of ion, possibly the ATPase system. The increased binding of potassium to actomyosin caused by cardiac glycosides[44] could result in changes in the physical properties of the contractile protein as demonstrated by Szent-Gyorgyi.[49] Braunwald and Klocke's postulate that potassium and digitalis may both alter the intracellular

distribution of calcium although appealing can neither be confirmed nor denied at this time

The findings by Ebert and associates that elevation of serum potassium results in a decrease in the content of tritiated digoxin in the canine heart could also partly explain the potassium induced digitalis antagonism

It is important to stress that in this study the effects of varying concentrations of potassium before and after the administration of ouabain were obtained with *each muscle serving as its own control* Muscle strips which did not return to base-line tension after exposure to high concentrations of potassium were not studied Since the initial conditions may vary greatly with different muscles these controlling features would enhance the likelihood of detecting the significant resultant changes. In this study force and peak dF dt varied in a closely proportionate fashion and neither of these measures of contractility was more responsive to a change in potassium or the addition of ouabain than was the other

Although it has been suggested that the core of rapidly contracting muscle strip may become hypoxic the marked stability of this preparation would indicate that hypoxia if present is insignificant In these experiments it seemed to be unwise to decrease myocardial metabolic requirements by lowering the temperature of the bath since hypothermia has previously been shown to decrease the flux of potassium and to impair the effect of digitalis on the egress of cellular potassium

It is apparent that the data presented can be viewed in two different ways. We have chosen to consider the effects of various concentrations of potassium on the inotropic action of ouabain. It is clear however that this study might equally well consider the influence of ouabain on the inotropic action of potassium Thus, ouabain can be shown to augment the negative inotropic effect of high levels of extracellular potassium but to have only an additive influence on the positive inotropic effect of low concentrations of potassium It seems to be probable that myocardial contractility depends on the algebraic sum of all the positive and negative inotropic factors acting upon the muscle at a given time and therefore that either method of viewing the data is equally applicable

Summary

The effects of varying concentrations of extracellular potassium on the positive inotropic action of ouabain were studied in an isolated muscle preparation of guinea pig right ventricles. The isometric tension and peak dF dt were significantly greater at a concentration of extracellular potassium of 2 mEq per liter than at the normal concentration of 5 mEq per liter in control studies. There was no significant difference between the tensions or maximum dF/dt at 5 and 10 mEq per liter potassium Ouabain produced a significant increase in tension and peak dF dt at all concentrations of potassium The ouabain induced increase in tension at 2 mEq per liter potassium was not significantly different from that at 5 mEq per liter but the level of attained tension and dF dt were greater at 2 mEq per liter since the base-line tension and dF/dt at this concentration were greater The positive inotropic effects of ouabain and low concentrations of extracellular potassium were therefore additive At a potassium of 10 mEq per liter the increment in tension and peak dF dt produced by ouabain was significantly less than at 5 mEq per liter and the absolute tension at 10 mEq per liter was also significantly smaller Possible mechanisms to explain these findings are considered

REFERENCES

1 Calhoun J A and Harrison T R Studies in congestive failure IX. The effect of digitalis on the potassium content of the cardiac muscle of dogs, J Clin Invest 10 139 1931

2 Friedman M and Bine R Observations concerning the influence of potassium upon the action of a digitalis glycoside (lanatoside C), Am J M Sc 214 633, 1947

3 Wood, E. H and Moe G. K. Correlation between serum potassium changes in the heart lung preparation and the therapeutic and toxic effect of digitalis glycosides, Am. J Physiol. 129 499 1940.

4 Sekul, P N and Saunders, P R Effect of therapeutic and toxic concentrations of ouabain upon potassium content of myocardium Proc Soc. Exper Biol & Med. 106 639 1961

5 Klein, R L and F m, M L Effects of

ouabain, hypothermia and anoxia on cation fluxes in embryonal chick heart, Am. J. Physiol. 200:735, 1961

6. Lee, K. S., Yu, D. H., Lee, D., and Burstein, S. G.: The influence of potassium and calcium on the effect of ouabain on cat papillary muscles, J. Pharmacol. & Exper. Therap. 132:139, 1961

7. Lee, K. S.: Relation of cations to the inotropic and metabolic action of cardiac glycosides. Proceedings of First International Pharmacological Meeting, Vol. 3, New Aspects of cardiac glycosides, edited by B. Uvnas, New York, 1963, The Macmillan Co., p. 185

8. Muller, P.: Ouabain effects on cardiac contraction, action potential, and cellular potassium, Circulation Res. 17:46, 1965

9. Regan, T. J., Talmers, F. N., and Hellems, H. K.: Myocardial transfer of sodium and potassium. Effect of acetyl strophanthidin in normal dogs, J. Clin. Invest. 35:1220, 1956.

10. Cairns, A. B., Loire, W. D., and Burch, G. E.: The effect of acetyl-strophanthidin on the kinetics of potassium and the Rb[86] in the myocardium of dogs, Am. Heart J. 59:404, 1960

11. Conn, H. L.: Effects of digitalis and hypoxia on potassium transfer and distribution in the dog heart. Am. J. Physiol. 184:548, 1956.

12. Schreiber, S.: Potassium and sodium exchange in the working frog heart, Am. J. Physiol. 185:337, 1956

13. Grupp, G., and Charles, A.: Effect of ouabain and 3-acetyl strophanthidin on potassium exchange in the dog heart in situ, J. Pharmacol. & Exper. Ther. p. 113:356, 1964

14. Boyer, P. K., and Poindexter, C. A.: The influence of digitalis on the electrolyte and water balance of heart muscle. Am. Heart J. 20:586, 1940

15. Vick, R. L.: Effects of some steroid and nonsteroid lactones on potassium exchange and physiological properties of the isolated perfused guinea pig ventricle, J. Pharmacol. & Exper. Therap. 125:40, 1959

16. Brown, T. E., Acheson, G. H., and Grupp, G.: The saturated lactone glycoside dihydroouabain. Effects on potassium balance of the dog heart, J. Pharmacol. & Exper. Therap. 136:107, 1962

17. Brown, T. E., Grupp, G., and Acheson, G. H.: The effect of quinidine on the potassium balance of the dog heart, J. Pharmacol. & Exper. Therap. 133:84, 1961

18. Leonard, E., and Hajdu, S.: Handbook of physiology. Section 2, Circulation, Vol. 1 (American Physiological Society), Baltimore, 1962, Williams & Wilkins Co., p. 186

19. Loewi, O.: Über den Zusammenhang zwischen Digitalis und Kalzium wirkung, Arch. exp. Path. Pharmakol. 82:131, 1917

20. Sampson, J. J., Albertson, E. C., and Kondo, B.: The effect on man of potassium administration in relation to digitalis glycosides, with special reference to blood serum potassium, the electrocardiogram, and ectopic beats, Am. Heart J. 26:164, 1943.

21. Enselberg, C. D., Simmons, H. G., and Mintz, A. A.: The effect of potassium upon the heart with special reference to the possibility of treatment of toxic arrhythmias due to digitalis, Am. Heart J. 39:713, 1950

22. Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E.: Interrelation between potassium metabolism and digitalis toxicity in heart failure, Proc. Soc. Exper. Biol. & Med. 76:797, 1951

23. Lown, B., Black, H., and Moore, F. D.: Digitalis electrolytes and the surgical patient, Am. J. Cardiol. 6:309, 1960.

24. Vassalle, M., and Greenspan, K.: Effects of potassium on ouabain-induced arrhythmias, Am. J. Cardiol. 12:692, 1963

25. Page, E.: The action of cardiac glycosides on heart muscle cells, Circulation 30:237, 1964

26. Schreiber, S. S., Oratz, M., and Rothschild, M. A.: Effect ouabain on potassium exchange in the mammalian heart, Am. J. Physiol. 200:1055, 1961

27. Holland, W. C., and Sekul, A.: Influence of K and Ca on the effect of ouabain on Ca entry and contracture in rabbit atria, J. Pharmacol. & Exper. Therap. 133:288, 1961

28. Garb, S., and Venturi, V.: The differential actions of potassium on the therapeutic and toxic effects of ouabain, J. Pharmacol. & Exper. Therap. 112:94, 1954.

29. Leonard, E., and Hajdu, S.: The effect of potassium on the inotropic action of cardiac glycosides, Circulation Res. 7:19, 1959

30. Leight, L., Roush, G., Rafi, F., and McGraff, C. J.: The effect of intravenous potassium on myocardial contractility and cardiac dynamics, Am. J. Cardiol. 12:686, 1963.

31. Williams, J. F., Klocke, F. J., and Braunwald, E.: Studies on digitalis. XIII. A comparison of the effects of potassium on the inotropic and arrhythmia-producing action of ouabain, J. Clin. Invest. 45:346, 1966

32. Feigen, G. A., Masuoka, A., Clinton, H. T., Saunders, P. R., and Sutherland, G. B.: Mechanical response of the isolated electrically driven rat ventricle strip, Stanford M. B. 10:27, 1952.

33. Noble, F. W.: Electrical methods of blood pressure recording, Springfield, Ill., Charles C Thomas, p. 41

34. Worcester, J.: The statistical method, New England J. Med. 274:27, 1966.

35. Koch-Weser, J., and Blinks, J. R.: The influence of the interval between beats on myocardial contractility, Pharmacol. Rev. 15:601, 1963

36. Hajdu, S., and Leonard, E.: The cellular basis of cardiac glycoside action, Pharmacol. Rev. 11:173, 1959

37. Hajdu, S.: Mechanism of staircase and contracture in ventricular muscle, Am. J. Physiol. 174:371, 1953

38. Greer, J. P., Carmain, N. J., and Sulkin, W. T.: Combined effect of calcium and potassium on contractility and excitability of the mammalian myocardium, Am. J. Physiol. 173:374, 1953

39. Garb, S.: The effect of potassium, ammonium

calcium strontium nd magnesium on the electrocardiogram nd myogram of mamm lia heart muscle J Pha macol & Expe Therap. 101:317 1951
40. Sze t Gyorgyi, A Chemical physiology of contraction body nd heart muscle New York, 1953 Academic Press, Inc p 27
41 Cotton, M nd Stopp, I Action of dig talis on the non-failing heart of the dog Am J Phy iol 192 114 1958
42 Braunwald E Bloodwell R D Goldberg L I nd Morrow A G Studies on dig talis. IV Observations in ma on the effects of dig talis preparat ons on the cont actil ty of the non-f iling heart nd on total v sc lar resistance J Clin. Invest. 40:52 1961
43 Mason D T and Bra nwald, E. Studies on digitalis. IX Effect of ouabai on the non-f iling human heart J Clin. Invest 42 1105 1963.
44 Burstein, S. G Bennett L L., I yne F E and Hopper J Effect f potassium nd lanatoside-C on th f iling heart in heart lung preparation I ed. Proc. 8:20 1949
45 N yler W G The effect of potassium on the response of th isolated heart t strophanthin-G, Australa ian J Exper Biol. 36:323 1958.
46. Waser P Cardiac glycosides and actomyosin, Proceedings of First International Pharmacological Meet ng Vol 3 p. 173
47 Braunwald E and Klocke F J : Digitalis, Annual Review of Medicine edited by A. C. DeGraff and W P Creger Menasha, Wis. 1965 George Ba ta Publishing C p. 371
48. Ebert, P A., Greenfield L. J nd Austin, W B. The effect of increased serum potassium on the digoxin content of the canine heart B ll Johns Hopkins Hosp 112 151 1963.
49 Tuttle R S Witt, P N and Farah, A. Therapeutic nd toxic effects of ouabain on K fluxes I rabbit tria, J Pharmacol. & Exper Therap 137:24 1962

Hemodynamic effects of isotonic solutions rapidly injected into the heart and great vessels

L. Jerome Krovetz, M.D. Ph.D
Robert W. Benson
Terry Neumaster B.A
Gainesville Fla.

Angiocardiographic contrast media have long been employed for delineation of intracardiac and intravascular anatomy. More recently a number of investigators have utilized contrast media in investigations of cardiovascular hemodynamics.[1-4] An unstated assumption of these latter studies is that rapid injection of contrast media has a negligible effect on the hemodynamic status of the subject. However it seems to be unlikely that the injection of volumes approaching and often exceeding the stroke volume of the heart over the course of a few heartbeats should cause no significant changes in the circulation.

Indeed such effects have been observed and are clearly separable into two areas. The first of these namely the effects of rapid injection of isotonic solutions into the heart and great vessels, is dealt with in this paper. Studies of the second type of hemodynamic effects, namely those due to the hypertonicity of angiocardiographic contrast media have been reported by other authors.[5-7] We were able to find only one previous study defining the consequences of rapid injections of isotonic solutions under conditions similar to those of angiocardiography. It is pertinent therefore to report our findings indicating that the effects of such injections are not neglibible.

Methods and materials

Adult mongrel dogs weighing between 10 and 20 kilograms were anesthetized with pentobarbital approximately 30 mg per kilogram intravenously. A No. 7F 50-cm N.I.H. catheter was used for all injections to insure comparability of the delivery system. Respirations were monitored by means of a thermocouple placed in an endotracheal tube while the dogs were allowed to breathe spontaneously.

Injections of fluids were made with a hydraulic injector.† The pressure gauge of the injector was calibrated against a manually operated test gauge.‡ The pressures as stated in this paper are those of the Cordis gauge dial pressure. This pressure is not exactly the same as that in the injection cylinder since the effects of the return spring were not subtracted. In addition the hydraulic accumulator does not maintain a constant pressure during the actual injection. Therefore the pressures

From the Department of Pediatrics, J. Hillis Miller Health Center University of Florida, Gainesville, Fla.
Supported in part by grants from the Florida Heart Association and the National Institutes of Health the Developmental Physiology Training Grant (T HD-341), and the Cardiovascular Training Grant (T-HE 5493-04 (5)).)
Received for publication June 21 1964.
*Recipient of Research Career Development Award K3-9741-01A
†Cordis Intercalative Angiograph, Cordis Co., Miami, Fla.
‡ Ashton Company Boston, Mass.

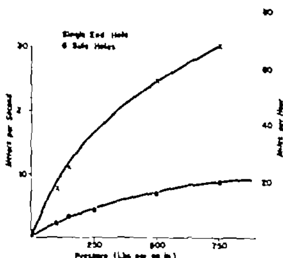


Fig. 1. Average velocity of injection of physiologic saline (0.9 per cent) through No. 7 French 50-cm. U.S.C.I. catheter at various pressures. The top line refers to the mean cross-sectional velocity through a single end-hole catheter whereas the lower line refers to average velocity through the side holes near the end of an N.I.H. catheter.

as listed in the paper should be regarded only as being relative to each other and will not correspond exactly to those of other injectors, except perhaps fortuitously. Rates of delivery varied according to the pressure of injection but ranged from 10 to 25 ml. per second with corresponding velocities of from 15 to 30 meters per second (Fig. 1).

Cardiac outputs were determined prior to each injection and at intervals from 1½ to 10 minutes after injection using indicator-dilution techniques.

Catheters used for pressure monitoring were flushed with heparinized saline prior to each injection and recording. If a step-up of pressure to 300 mm. Hg showed the catheter system to be overdamped, the catheter was either cleared or replaced. Continuous pulmonary arterial and femoral arterial pressures were recorded for a minimum of 5 minutes after each injection. Pressures, injection markers, respirations, and other data were recorded on an ultraviolet oscillographic recorder.*

After the catheters were in place, systemic arterial pressure, pulmonary arterial pressure, and respirations were recorded for approximately 5 minutes in order to establish base-line values. Maximum reactions were measured at the point of maximum difference in pressure from that preceding the injection. Recovery times were defined as time from injection until the pressure in question returned to within 2 mm. Hg of preinjection levels. All pressures were measured during expiration for comparability.

*Honeywell Visicorder Model 1108, Heiland Division, Denver, Colo.

Results

Injections into the right heart. Injections into the right atrium or right ventricle were studied in 10 dogs. Fig. 2 is a record of a representative right atrial injection whereas Fig. 3 shows a typical response after injection into the right ventricle. Systemic arterial pressures showed a period of brief hypotension followed by hypertension and usually then a second longer period of hypotension. Pulmonary arterial pressure increased in all except one instance to an average of 9 per cent above the control values. Pulmonary arterial capillary pressure decreased in only one instance; in the other 4 cases in which it was measured there was no significant change. Systemic arterial pressure took an average of 22 seconds to return to within 2 mm. Hg of control values whereas pulmonary arterial pressure averaged 43 seconds to recovery. Cardiac outputs increased to an average of 21 per cent over the control values but returned to control values within 2 minutes after injection.

There was no effect on respiratory rate. Virtually all of the injections were followed by one or two premature contractions.

Injections into the left heart. Ten injections of normal saline were made into the left heart. In each instance the amount was 1 c.c. per kilogram of body weight and the injection pressure was 750 pounds per square inch (p.s.i.). Injections were made into the left ventricle, aortic root, arch of the aorta, and descending thoracic aorta. Except for the occurrence of premature ventricular contractions after ventricular injections, no essential differences were seen. Therefore the data were grouped and treated under the collective term of left heart injections.

In general, the effects of left heart injec

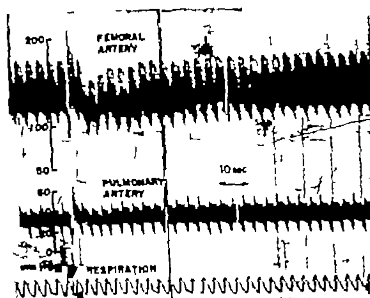


Fig. 2. An example of the effects of injection of 1 c.c. per kilogram of normal saline, at 750 p.s.i., into the right atrium. The small arrows indicate the time of return of systemic systolic and diastolic pressures to within 2 mm. Hg of preinjection values. The large arrow indicates the time of injection, which is also indicated by the galvanometer beam immediately below the respiration waveform. Two premature contractions are followed by systemic and pulmonary arterial pressure transients, then a rise in both pulmonary and systemic arterial pressure, and finally a fall in systemic arterial pressure.

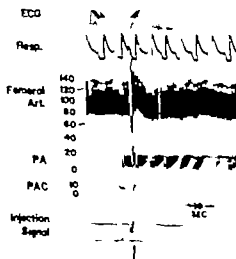


Fig. 3. Dog No. 37, 10 kilograms. Typical hemodynamic response to injection of 1 c.c. per kilogram of normal saline at 750 p.s.i., into the right ventricle. Except for the occurrence of premature ventricular contraction, the results are similar to those after injection into the right atrium.

tion were more striking than those of right heart injection (Figs. 4 and 5). In every instance this produced an immediate but transient increase in systemic pressure followed by a period of hypotension before a return to preinjection pressures. Systemic arterial pressures dropped an average of 31 per cent below the control values, whereas pulmonary arterial and pulmonary arterial capillary pressures increased 33 and 32 per cent, respectively. Recovery times averaged 31 seconds for the systemic artery and 69 seconds for the pulmonary artery. Cardiac outputs were more variable than after right heart injections. One dog showed a maximum increase of 32 per cent above the control value; the others showed decreases ranging from 1 to 40 per cent. Cardiac outputs were slower to return to preinjection levels, requiring about 6 minutes. The effects on the rate of respirations or heartbeat were extremely variable but most commonly produced tachypnea and bradycardia and or extrasystoles.

Thus all measured parameters returned to normal within 6 minutes. No significant differences were noted for rates of injection

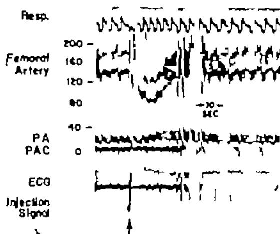


Fig 4 Dog N 46 13 kilograms. Typical example of the effects of injection of 1 per kilogram of normal saline (0.9 per cent) into the left ventricle. Injection pressure was 750 p.s.i. through 50-cm No. 7F N I H catheter (In this and all subsequent figures the time lines are at 10-second intervals.) Note the transient rise in pressure after injection which reaches a maximum of 40 mm Hg. Immediately thereafter systemic arterial pressure declines and pulmonary arterial pressure rises.

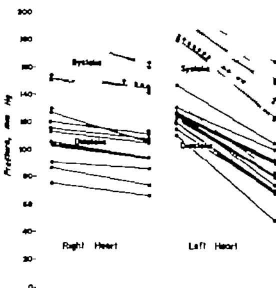


Fig 5 Comparison of the effects on systemic arterial pressure of injection of normal saline into the left and right heart (1 c.c. per kilogram through No. 7F N I H catheter at 750 p.s.i.). The responses to injection into the left ventricle, aortic root, aortic arch or descending aorta were all comparable as were the injections into the right atrium or right ventricle. Injections into the right side of the circulation produced only about half of the response that followed injection into the left side. This was also true for the effect on systemic arterial recovery time, pulmonary arterial pressure, and pulmonary arterial recovery time. The larger dots and heavier lines refer to the averages of each group.

into the left ventricle, root of the aorta, arch of the aorta, or descending aorta.

Effects of varying injection pressures. Figs. 6 and 7A show the effect of varying injection pressures. The amount injected was 1 c.c. per kilogram and the site of injection was the aortic root. There were several correlations of the data shown in these figures and increasing pressure. Note first that the initial injection transient increases with increasing pressure. The minimum pressure reached also increased with increasing pressure as did the systemic arterial recovery time. In one series of experiments there was a similar correlation of pulmonary arterial pressures and pulmonary arterial recovery times. This effect was not so consistent in other dogs as the effect on systemic arterial pressure.

Effects of varying the amount injected. Fig. 7B illustrates the converse of the above-mentioned situation, with injection pressure held constant at 750 p.s.i. and the amount injected increased from 0.5 to 2 c.c. per kilogram. There was little correlation of the various parameters measured with increasing amounts of injectate except for systemic arterial recovery time.

Effects of injection of other isotonic solutions. A solution of 5 per cent dextrose in water was injected into the right atrium of 3 dogs. These animals demonstrated an increase in systemic arterial pressure over control values, averaging 6 per cent above resting values, whereas pulmonary arterial pressures rose 13 per cent over control values. Pulmonary arterial capillary pressures showed no change. The recovery times for systemic arterial pressure averaged 11 seconds, whereas those for pulmonary arterial pressure averaged 8 seconds. Cardiac outputs showed no significant change from preinjection values.

In dogs, 1 c.c. per kilogram of the animal's own blood was withdrawn into a prewarmed syringe and then injected at 250, 500, 750 p.s.i. into the root of the aorta (Fig. 8). In every instance systemic arterial pressure dropped and pulmonary arterial pressure rose. Pulmonary arterial capillary pressure was essentially unchanged. Systemic arterial recovery times were strikingly prolonged as compared to those after normal saline at comparable

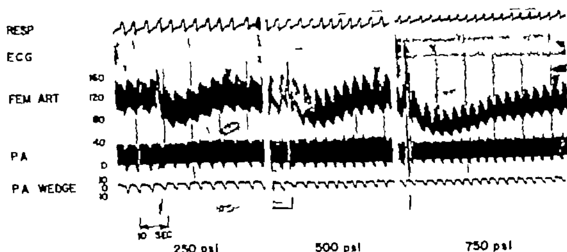


Fig. 6 Dog No. 34 12 kilograms. The effects of injecting the same volume of normal saline (1 c.c. per kilogram) at increasing pressures into the aortic root. The peak systemic arterial pressure, minimum systemic arterial pressure, and the systemic arterial recovery time all increase with increasing pressure of injection. Similar changes were noted for the pulmonary arterial pressure but these are not so obvious in the small-scale reproduction.

pressures. For example, when 750 p.s.i. was used, the systemic arterial recovery time after injection of normal saline averaged 31 seconds, whereas after the injection of blood it averaged 232 seconds.

Injection of isotonic solutions in human beings. In the course of routine cardiac catheterizations in 11 subjects without shunts, 1 c.c. per kilogram of normal saline was injected at 750 p.s.i. into the right atrium or pulmonary artery. Angiocardiographic catheters, varying from 80 to 100 cm. in length and 1.09 to 1.4 mm. in internal diameter, were employed. As in the animal experiments, cardiac outputs were determined by indicator-dilution techniques immediately prior to and from 2 to 5 minutes after injection. ECG, systemic arterial pressure, and usually pulmonary arterial pressures were monitored.

A typical study is shown in Fig. 9. Note the immediate decline in systemic arterial pressure and the rise in pulmonary arterial pressure. There were no differences between the observed effects of injection in human beings and those cited earlier in the dogs studied.

Discussion

The volumes injected and the injection pressures employed were similar to those commonly employed in angiocardiography. At least part of the discrepancy between our results and those of earlier investigators undoubtedly lies in a difference in the rates of injection. Thus, Nakanishi and associates[11] found no significant hemodynamic changes after the injection of 0.5 to 1.0 ml. per kilogram of normal saline over a period of 2 to 5 seconds. Our volumes ranged from 0.5 to 2.0 ml. per kilogram and were injected in less than 2.5 seconds, probably representing a doubling of the velocity of injection.

Although a number of investigators have reported on the effects of rapid injections of hypertonic solutions,[11] far less information is available concerning the effect of rapid injections of isotonic solutions.[7, 10, 11] During the course of a study of the hemodynamic effects of angiocardiographic contrast media, it became apparent that the effects of rapid injection of isotonic and hence presumably less toxic solutions would have to be separated from those due to the effects of hypertonicity. It should be noted that the angiographic contrast media generally employed range from 1,360 to ,373 mOsm. per liter.

Read and associates studied the effect of distilled water, 5 per cent glucose, 0.9 per cent saline, and isotonic NaOH in 8

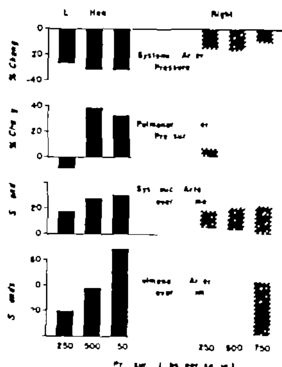


Fig 7A Comparison of the effect of increasing pressure of injection and the amount of injection. (I jection 1 per kilogram through No. 7I 50-cm. NIH catheter.) Fourteen injections to the left heart at increasing pressures showed increasing average effect on the maximal changes in systemic arterial and pulmonary arterial pressures. In contrast the 12 injections to the right heart showed lesser changes with only systemic arterial recovery times increasing with increasing injection pressure.

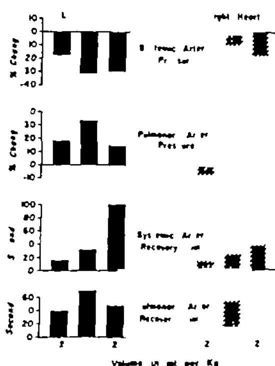


Fig 7B Comparison of 16 left and 13 right heart injections (through No. 7F 50-cm NIH catheter at 750 p. s. i.) of increasing volumes. There is no corresponding increase in average maximal pulmonary arterial pressure response or recovery time. The systemic arterial recovery times after both right and left heart injections show a good correlation with the increasing volume of injectate.

dogs. Rates of infusion ranged from 05 to 1 ml per second They noted an average decrease in systemic arterial pressure of 10 per cent. Both Andres and co-workers[13] and Crowley and his group[3] noted an increase in cardiac output after the rapid injection of saline into the brachial artery and aorta respectively They attributed this to the release of ATP from erythrocytes damaged by the high energy of the saline injectate. The velocity of saline injections (Fig 1) is many times that of arterial blood flow

The effects of rapid injection of isotonic solutions may be divided into three areas. First they *commonly cause arrhythmias* most usually atrial or ventricular premature contractions. These occur almost immediately after injection and are probably due to a direct irritant action of the high-velocity stream These *arrhythmias result in a brief period of irregular heart* action and a transient fall in systemic and pulmonary arterial pressures. The general effect on hemodynamics is transient although occasional premature contractions continued for a minute or longer after injection in a few cases (Fig 4)

A second effect is to cause transient local increases in pressure These were *almost universally seen and* lasted for approximately two or three heart cycles. Part of these recorded elevations may have been due to the injectate striking the pressure monitoring catheter The maximum height reached was related to the pressure of injection and hence should be *considered to be a real physical* phenomenon although the exact magnitude of the change in pressure is open to argument

It is likely that these two phenomena in turn produce the third effect, when

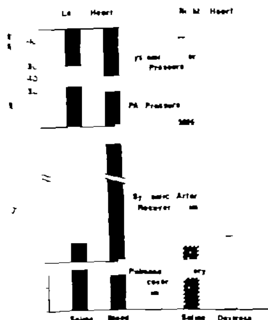


Fig. 8. Comparison of the effects of rapid injection of three isotonic solutions (1 c.c. per kilogram at 750 p. i. through No. 7F 50-cm. N.I.H. catheter). The effects of injection of 5 per cent dextrose in water are similar to those seen after the injection of 0.9 per cent saline. The effects of injecting the dog's own blood into the aorta are similar to those after injection of normal saline, except for the considerably longer time required for the systemic arterial pressure to return to control values.

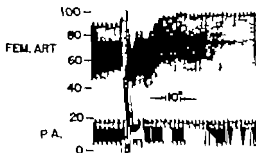


Fig. 9. Effect of rapid injection of 0.9 per cent NaCl (1 c.c. per kilogram at 750 p.s.i.) into the main pulmonary artery of 13-year-old girl with complete repair of ventricular septal defect. Note the similarity to the reactions in dogs. There are immediate and dramatic changes in both femoral and pulmonary arterial pressures, which returned to preinjection values approximately 3 minutes after injection.

more prolonged changes in pressure and flow occur. During this phase, there is a fall in systemic arterial pressure and less regular changes in pulmonary arterial and pulmonary capillary pressures. The depth and duration of the changes in systemic arterial pressure depend on the pressure of injection, the volume of the injectate, and the site of injection being about twice as great for injections on the left side of the heart. Changes in pulmonary arterial and pulmonary capillary pressures were less striking for right heart injections. Part of these differences may have been due to the scale factor selected, which rendered it more difficult to read changes in pulmonary arterial or pulmonary capillary pressure with a degree of accuracy comparable to the reading of systemic arterial pressures.

There appear to be two possible explanations for this latter phase: first, this represents stimulation of baroceptors, particularly aortic arch and carotid sinus receptors, and secondly, this results from the destruction of erythrocytes, which release ATP that in turn leads to peripheral vasodilatation and pulmonary arteriolar constriction.[13,1] The prolonged recovery times after the injection of blood would suggest that the destruction of erythrocytes plays a major role. In 2 animals which were vagotomized and in 1 additional atropinized animal, systemic arterial pressure rose an average of 12 per cent, whereas pulmonary arterial pressure increased nearly four times as much as in the animals with normal vagal response.

Friesinger and associates found no hemolysis on spectrophotometric examination of samples of blood obtained after angiocardiography. However, it appears that extremely minute amounts of hemolysis can be responsible for marked hemodynamic changes. It is possible that the spectrophotometric methods employed in their study were not sufficiently sensitive to detect hemodynamically significant amounts of red-cell destruction.

An ingenious explanation for the effect of the site of injection has been advanced by Hallermann, Rastelli, and Swan. After right ventricular injection they noted a relatively constant time interval to the

onset of an increased left ventricular stroke volume. This led them to postulate that the injected volume acts as a competitor for the ventricular filling by preventing inflow from the atrium. Although these investigators employed heparinized blood as the injectate, their results were similar to those of this study.

It would seem that the rapid injection of even such benign substances as 0.9 per cent sodium chloride, 5 per cent dextrose, or heparinized blood is capable of causing significant immediate and virtually unpredictable hemodynamic changes. In this regard, the reported discrepancy between cardiac outputs calculated by measuring ventricular volumes by angiocardiography and by indicator-dilution techniques is worthy of emphasis.[13] The changes produced in this study were immediate and extended throughout the time period of interest during angiocardiographic examinations. Extrapolation of physiologic data from angiocardiographic examinations should be made only with great caution. As a minimum requirement, the electrocardiogram, *respirations*, and appropriate vascular pressures should be monitored during the recording of an angiocardiogram and the physiologic data weighed accordingly.

Summary

Rapid injections of 0.9 per cent NaCl, 5 per cent dextrose, and heparinized blood were made into the heart and great vessels of dogs under conditions mimicking those of angiocardiography. Injections into the right side of the heart were usually followed by alternating periods of systemic hypotension and hypertension, an increase in pulmonary arterial pressure, and an increase in cardiac output. Injections into the left ventricle and aorta were more striking. Systemic arterial pressures decreased by an average of 31 per cent of control values, whereas pulmonary arterial and pulmonary arterial capillary pressures increased approximately the same amount. Changes in cardiac output were variable, ranging from +35 to −40 per cent of control values. Left heart injections also produced tachypnea, bradycardia, and extrasystoles in several of the dogs. Similar effects were demonstrated in 11 patients undergoing diagnostic catheterizations.

In view of the fact that these effects could be produced by the rapid injection of isotonic solutions, considerable caution should be observed in extrapolating physiologic data from angiocardiograms.

We wish to acknowledge the technical help of Schuyler Hardin, Mary Overfield, Barry Mitchell, Virginia Morgan, J. Graetz, and Warren Tierney. We would also like to thank Betty Sutterer for her excellent editorial assistance. We are also indebted to Dr. Gerold I. Schiebler and Dr. Richard T. Smith for their aid in reviewing this manuscript.

REFERENCES

1. Bruce, T. A., Chapman, C. B., Baker, O., and Fisher, J. N.: The role of autonomic and myocardial factors in cardiac control, J. Clin. Invest. 12:1721, 1963.
2. Lind, J., and Wegelius, C.: Human fetal circulation: Changes in the cardiovascular system at birth and disturbances in the post-natal closure of the foramen ovale and ductus arteriosus, Cold Spring Harbor Symposium on Quantitative Biology 19:109, 1954.
3. Meyer, J. A., Figley, M. M., Haight, C., Sloan, H. F., Ellsworth, W. J., Jr., and Bobbitt, D. E.: Coronary arteriography as a physiologic investigational technique, J. Appl. Physiol. 16:878, 1961.
4. Miller, G. A. H., Kirklin, J. W., Rahimtoola, S. H., and Swan, H. J. C.: Volume of the left ventricle in tetralogy of Fallot, Am. J. Cardiol. 16:488, 1965.
5. Cotran, E. S.: Cardiac blood pressure and respiratory effects of some contrast media. The dangers of overdose, Acta Radiol. (Suppl.) 116:58, 1954.
6. Eliakim, M., Rosenberg, S. Z., and Braun, K.: Effect of hypertonic saline on the pulmonary and systemic pressures, Circulation Res. 6:357, 1958.
7. Read, R. C., Johnson, J. A., Vick, J. A., and Meyer, M. W.: Vascular effect of hypertonic solutions, Circulation Res. 8:538, 1960.
8. Gammona, S. T., Lurie, P. R., and Segar, W. E.: Hypertonicity following selective angiocardiography, Circulation 28:1096, 1963.
9. Friesinger, G. C., Schaffer, J., Criley, J. M., Goertner, R. A., and Ross, R. S.: Hemodynamic consequences of the injection of radiopaque material, Circulation 31:730, 1965.
10. Hallermann, F. J., Rastelli, G. C., and Swan, H. J. C.: Effects of rapid injection of heparinized blood into right and left ventricles in dogs, Radiology 83:647, 1964.
11. Nakanishi, A., Sugiura, M., Takabatake, Y., Ito, I., Tsuyuki, H., Ohta, A., Yasoda, H., and Ueda, H.: Circulatory and respiratory effects of hypertonic saline, with special reference to the coronary effect, Jap. Heart J. 2:77, 1961.
12. Andres, R., Zierler, K. L., Anderson, H. M.

Stainsby, W. N., Cader, G., Ghrayyib, A. S., and Lilienthal, J. L., Jr.: Measurements of blood flow and volume in the forearm of man with notes on the theory of indicator-dilution and on production of turbulence, hemolysis, and vasodilatation by intra-vascular injection, J. Clin. Invest. 33:482, 1954.

13. Crowley, W. P., Jr., Grace, J. B., Fox, I. J., and Wood, E. H.: A depressor reaction caused by forceful intra-arterial injections in the descending aorta of man, (Abstract) Circulation 12:691, 1955.

14. Bernstein, E. F., Reller, C. R., and Craig, T. B.: Experimental studies of Angio-Conray: A new angiographic agent, Radiology 79:589, 1962.

15. Miller, G. A. H., and Swan, H. J. C.: Effect of chronic pressure and volume overload on left heart volumes in subjects with congenital heart disease, Circulation 30:205, 1964.

Case reports

The isolated systolic click with bacterial endocarditis

E. Joseph LeBauer, M.D.
Joseph K. Perloff, M.D.
Thomas F. Keliher, M.D.
Washington, D.C.

Systolic clicks were described by Gallavardin[1] in 1913. Until the relatively recent past, these mid or late systolic clicking sounds (single or multiple) were believed to originate in the pericardium or contiguous extracardiac structures and accordingly were considered to be benign auscultatory signs.[2] The late systolic murmur that frequently (although not invariably) accompanied the systolic clicks was also considered to be a benign extracardiac event. However, current data convincingly support the view that both of the aforementioned acoustical events can originate in the mitral valve or its supporting structures. In patients with late systolic murmurs, mitral regurgitation has been clearly demonstrated,[3,4] and comment has been made in regard to the theoretical susceptibility to bacterial endocarditis.[5,11,12] Similar suspicion has not been applied to patients who have systolic clicks but no murmur. In fact, there are thus far no reported examples of bacterial endocarditis in subjects with either isolated late systolic murmurs, isolated systolic clicks, or combinations of these. We have recently observed a patient who was known to have had a systolic click (without murmur) for at least 6 years, who presented with classic evidence of bacterial endocarditis *after dental manipulation*, and who developed a late systolic murmur during the course of observation. The information is reported because of the implications of endocarditis occurring in an individual with an isolated systolic click.

Case report

The patient, a 56-year-old white man, was admitted to Georgetown University Hospital with a 4-week history of fever and lethargy. Six weeks prior to admission his teeth were cleaned during *routine* dental examination, and 2 weeks later he experienced the onset of diaphoresis, malaise, and anorexia. Two days before admission his fingertips became painful, and a tender, warm, red, swollen area appeared behind the left lateral malleolus. Arthralgias, headache, abdominal pain, and hematuria were not described.

There was a history of scarlet fever at age 5 years, but no other stigmata of rheumatic fever. Six years prior to admission, one of us (T. K.) detected a systolic click which was readily confirmed on each of many subsequent examinations, although a murmur was never heard.

Physical examination. The physical appearance was normal. Blood pressure was 135/80 mm Hg in

From the Department of Medicine, Georgetown University School of Medicine, and Division of Cardiology, Georgetown University Hospital, Washington, D. C.

This investigation was supported in part by United States Public Health Service Research Career Program Award K HE 14000 and by United States Public Health Service Grants HE 09093 and HE 3319 from the National Institutes of Health, Bethesda, Md.

Received for publication May 27, 1966.

Address: Georgetown University Hospital, 3800 Reservoir Rd., N.W., Washington, D.C., 20007.

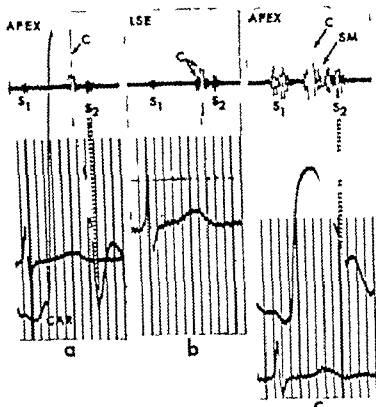


Fig. 1. Phonocardiograms taken t the pex nd lower left sternal edge (*LSE*), showing normal first nd second heart sounds (S_1 nd S_2) and loud late systolic lick (*C*) but no murmu *CAR* Carotid Phonocardiogram at pex. The click is now in mid ystole and introduces late sy tolic murmur (*SM*) See ext for details.

both arms The cardiac rate wa 100 per minute th regular rh thm nd occasional premature entric lar ontractions Ther er no petechiae in the fund on the mucous membr nes, or in the skin but n erythematous tender swollen area as present posterior to the left lateral malleolus The arterial nd jugular enous pulses er normal The lungs ere lear P ecordial palpation defined normal left entricular impulse. Auscultation t the pex re ealed prominent constant l te systolic click (Fig 1) A murmur could not be licited by exercise or by turning into the left l ter l decubitus position The click as ll t ans-m ted to the sternal edge and even the base (Fig 1) In the second lef intercostal pac the second heart sound as normal in both intensity and splitti ng The ip of a nontender spleen palpable beneath the lef costal margin. Sever l fingertips ere tender but neither digital lubbing nor splinter hemorrhages er present Neurological examinat as normal

Laborator data The hematocrit 4 per cent on admission but decreased t 38 per cent by the t fth hosp l day th subsequent return t normal The urin ed sedimen tion t as 30 mm per hour The hit blood cell ount 13 400 h 6 polymorphonuclear leukocy es, l band 20 l mphoc tes and 3 mono yt Proteinuria as

bsent but there was an erage of 4 to 5 red blood cells per high-power field on man examinations of the urinary sediment Febrile agglutinins ere nega tive The total protein as 6 3 Gm per 100 ml (3 7 Gm. albumin nd 2 6 Gm globuli) A total of 9 blood cultures as done ith *Streptococ us ridans* growing on ll plates. The organ sm as sensitiv to penicillin, lincom cin Keflin, nd streptom cin The electrocardiogram showed P R interv l of 0 16 second th no abnormalities of QRS ST seg ments, or T aves. Chest roentgenograms th ba ium esophagram evealed norm l ardiac silhouette

Course nd treatment During he 13 d of hospitalization the pa ien mper ure ose 103 F each evening On he f urth hosp l da (ter growth of *St ptococ us ida* from all blood cultures, int enous lincom 4 8 Gm dail) nd intramuscular st eptom 1 Gm each 12 hour) ere begun A er 4 da the st eptom as reduced to 0 5 Gm. each 12 hou nd as con tinued t hat level for the next 10 da The l nco mycin as on nued for otal of 26 da

Antim obial herapy as followed by defer escenc h 24 hour A low grade fe er per sisted for 5 da after h h he pa ien emained afebrile The tender swollen are lteh nd he lef

lateral malleolu lated but large subconj nctival hemorrhage appe red on the tenth hospital day fter which ther wa no further evidence of systemic emboli. Meticulou exam nations tw to three times daily revealed persistence of the late y tolic click without an ssociated m rmur On the tenth hospital day the lick for the f rst time in tated a Grade 2 (out of 6) high-frequency late systolic murmur that w best heard at the cardiac apex (Fig 1) The murmur persisted during the patie t s entire hospital ta but when the patient was reexamined a month fter discharge onl the lick wa heard

The phonocardiogram on admission (Fig 1,a b) howed the lat s tolic click w thout murmur The second phonocardiogram (Fig 1,c) how the subsequent appe rance of the murmur immediately after the sy tolic cl k (g increased for larity)

Discussion

Reid postulated that mid to late systolic clicks (to be distinguished from early systolic ejection sounds) might sometimes originate in abnormal chordae tendineae of the mitral valve The term chordal snap was coined to describe these clicking sounds. Barlow and associates supported Reid s postulation with a necropsy observation of a single fibrosed mitral chorda in a patient who had had an isolated mid systolic click In addition it was pointed out that such chordae tendineae may or may not be associated with mitral regurgitation Subsequent observations have clearly dem onstrated mitral insufficiency in patients with systolic clicks and late systolic mur murs. Although the history in these patients generally provides no clear etiology for the al normality of the mitral apparatus occasionally there is convincing evidence of prior rheumatic fever [13] and more recently a genetically determined defect in the posterior leaflet has been proposed [1] Al though it is attractive to relate our patient s antecedent history of scarlet fever to subsequent rheumatic chordal scarring this relationship is clearly speculative In view of the known susceptibility of a malformed (especially incompetent) mitral orifice to bacterial endocarditis attention has been called to the theoretical susceptibility of subjects with late systolic murmurs with or without accompanying clicks. [11] It is of particular interest that the patient whose case is described in this report developed convincing clinical evidence of endocarditis while manifesting an isolated systolic click. A late systolic murmur did in fact appear but only after the inception of endocarditis.

Extracardiac systolic clicks have been ascribed to mediastinal emphysema pericarditis,[7] pneumothorax [8] and the xyphosternal crunch [9] It is important to emphasize that although mid to late systolic clicks can have either an extracardiac or intracardiac origin there is, as a rule no reliable auscultatory means of distinguishing one type from another when they occur as isolated acoustical events.

Intracardiac phonocardiography can localize the source of the clicks,[10] but cardiac catheterization is generally inappropriate in view of the absence of additional evidence of heart disease The diagnosis of intra cardiac origin of the clicks is supported by the coexistence of a late systolic mur mur [9,11,14] It is appropriate to recommend prophylactic antibiotics for endocarditis in patients with late systolic murmurs, whether systolic clicks do or do not ac company these bruits. Although the case in this report represents the only known example of endocarditis occurring with an isolated systolic click susceptibility to en docarditis must be considered in this context since clinical information may not distinguish intracardiac from extracardiac clicks. It must be pointed out, however that no conclusions can be drawn with regard to the degree of susceptibility to endocarditis in subjects with isolated systolic clicks of intracardiac origin

Summary

The mitral valve and its supporting structures have been convincingly implicated as a source of late systolic murmurs as well as mid to late systolic (nonejection) clicks. Although attention has been called to theoretical susceptibility to endocarditis in subjects with these auscultatory signs, the patient whose case is described here represents the first example of the occur rence of endocarditis in this context. The endocarditis had its inception when only an isolated systolic click was heard A late systolic murmur appeared for the first time during the course of treatment In view of the difficulty in distinguishing intracardiac from extracardiac systolic clicks, consideration must be given to prophylaxis for endo-

carditis even when these mid to late systolic clicking sounds occur without an accompanying late systolic murmur

Addendum

Since this paper was submitted for publication Linhart and Taylor (*American Journal of Cardiology* 18:164, 1966) reported an instance of *Streptococcus viridans* endocarditis in a 37 year-old woman with a systolic click *and* a late systolic murmur. In addition one of us (J.K.P.) has seen *Streptococcus viridans* endocarditis in a 2 year-old woman with an isolated late systolic murmur

REFERENCES

1. Gallavardin, L. Pseudo-dédoublement du deuxième bruit du coeur simulant le dédoublement mitral par bruit extracardiaque télésystolique sur joint. Lyon Med. 121:409, 1913.
2. Leatham, A. Auscultation of the heart, Lancet 2:703, 1958.
3. Humphries, J. O. and McKusick, V. A. The differentiation of organic and "innocent" systolic murmurs, Prog. Cardiovas. Dis. 5:152, 1962.
4. Hamman, L. Spontaneous interstitial emphysema of the lungs, T. A. Am. Physicians 52:311, 1937.
5. Scadding, J. G. and Wood, P. H. Systolic clicks due to left-sided pneumothorax, Lancet 2:1208, 1939.
6. Schwab, L., Smiley, G. L., and Meyer, W. P. Xyphosternal crunch. Ann. Int. Med. 31:228, 1949.
7. McKusick, V. A., Webb, G. N., Humphries, J. O., and Reid, J. A. On cardiovascular sound. Further observations by means of spectral phonocardiography. Circulation 11:849, 1955.
8. McKusick, V. A. Cardiovascular sound, Baltimore, 1958, Williams & Wilkins Co., p. 181.
9. Brigden, W. and Leatham, A. Mitral incompetence, Brit. Heart J. 15:55, 1953.
10. Reid, J. V. O. Mid-systolic clicks, South African M. J. 35:353, 1961.
11. Barlow, J. B., Pocock, W. A., Marchand, P. and Denny, M. The significance of late systolic murmurs, Am. Heart J. 66:443, 1963.
12. Segal, B. and Likoff, W. Late systolic murmur of mitral regurgitation, Am. Heart J. 67:757, 1964.
13. Ronan, J. A., Perloff, J. K., and Harvey, W. P. Systolic clicks and the late systolic murmur. Intracardiac phonocardiographic evidence of their mitral valve origin, Am. Heart J. 70:319, 1965.
14. Barlow, J. B. and Bosman, C. K. Aneurysmal protrusion of the posterior leaflet of the mitral valve, Am. Heart J. 71:166, 1966.

Acquired cor triventriculare, a rare complication of cardiomyopathy

Lawrence S Cohen M D
Robert A Buccino M.D
William C Roberts M D
Bethesda Md

Primary myocardial disease is frequently complicated by mural thrombus formation Although intracavitary clot is suggested by previous pulmonary or systemic emboli mural thrombi are often not recognized until autopsy [1] The present report describes the clinical and pathologic features of a patient with primary myocardial disease in whom autopsy revealed a fibrin thrombus bisecting the left ventricular cavity into two separate compartments joined by several small communications. This form of curtain thrombus has not heretofore been reported yet its antemortem recognition could prove to be valuable in the management of a patient with *primary myocardial* disease. If angiography demonstrates this type of intracavitary thrombus surgical removal would undoubtedly improve cardiac hemodynamics and prove beneficial to a patient whose deteriorating course could be attributed to intracavitary clot.

Case report

D S. (05-97 76) 39-year-old laborer was well [til] September 1964 when exertional and nocturnal dyspnea orthopnea, nd peripheral edema developed These ma ifestations of cardiac failure disappeared after digitalis nd diuretic therapy but hile hospitalized he sustained embolus t the left subclavia artery I January 1965, he had an episode of hemoptysis which w subsequently ttributed to pulmonary emboli, nd he was admitted t the National Heart Institute. Cardiac catheterization disclosed a right entricular pressure of 20/2 mm. Hg, and resting left entricular pressure of 100/18 mm Hg rising to 122/33 mm Hg ith exercise There was no stolic pressure gradient between the left entricle and the aorta. The resting cardiac index as 2 06 liters per minut per square meter N angiogr phic tudies were performed On the basis of the history and catheterization f ndings diagnosis of primary myocardial disease was made

I April, 1965 he returned t f ll-time, strenuous employme t. H remained asymptomatic until December 1965 when he again developed pleuritic chest pai and hemoptysis. Fi weeks later he as readmitted t the National Heart Instit te because of episodes of dyspnea nd substernal chest pain, nd the development 1 week before admission, of ja ndice

On examination he ppeared to be acutely ill, wa dyspneic nd eating t rest, nd had cough productiv of purulent sputum The temperature was 38.5°C. The jugular veins were distended and ales were udible over the left lower lung posteriorly The cardiac impulse was not palpable. The pulmonic closure sound was accentuated and atrial and ventricular gallop sounds were present. A Grade 2/6 sy tolic ejection *murmur* was audible at the lower left sternal border The li er as enlarged and tender The hemoglobi was 15.4 Gm. per 100 mL, nd the whit cell ount as 17,200 per cubic millimeter ith 83 per ent neutrophils,

From the Cardiology Branch and Clinic of Surgery National Heart Institute Bethesda, Md.
Received for publication July 7 1966.
*Cardiology Branch, National Heart Institute, National Institutes of Health, Bldg. 10, Room 7B 15, Bethesda, Md. 20014

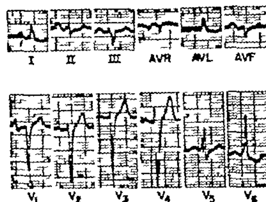


Fig 1 Electrocardiogram demonstrating an intraventricular conduction defect, subendocardial ischemia, and left atrial enlargement.

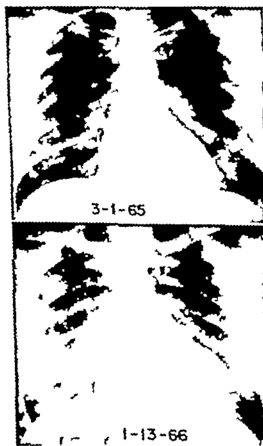


Fig Ches oent genogram. Ilter T ken 11 mon h before death Below I rtable ra film ken 40 da bef e de th The ardiac silhouett has enlarged durin his nterval, nd congesth pulmonary ch nges are present in the later radiogr ph

11 per cent l mphocytes, and 6 per cent monocytes. The blood urea nitrogen was 39 mg per 100 ml. serum bilirubin, 3.2 mg per 100 ml serum glutamic oxaloacetic transaminase 1,310 units serum glutamic pyruvic tran-aminase 1 119 units lactic dehydrogenase, 3 600 nits total serum protein 6.2 Gm per 100 ml., ith lbumin 3 7 Gm per 100 ml. serum am lase 69 units l prothrombin time 20 5 seconds ith control of 14 0 seconds.

The electrocardiogram (Fig 1) showed sinus tachycardia with frequent premature entricular contractions, left trial enlargement intra entricular conduction defect, and subendocardial ischemia The chest roentgenograms (Fig. 2) showed ardiomegaly and pulmonary scular congestion

Diuretic and antibiotic therapy as instit ted and his ondition improved. On the third hospital da however right-sided pleuritic chest pain ssociated ith pleural friction rub nd hemopt sis, suddenly developed, and he was treated th heparin Because of recurrent episodes of severe chest pain associated ith dyspnea, h potension, tachycardia, cyanosis and peripheral asoconstriction diagnosis of ecurrent pulmonary embol seemed to be justified, and ligation of the inferior ena ca was performed on the twent -first hospital da His ond tion however did not impro Gastrointestinal bleeding became eviden on the thirty-ninth hospital day and h died 1 da later

At necropsy (A66-31) the heart eighed 720 grams, and all chambers ere enlarged (Fig 3) The walls of both the right and the lef entricle were h pertrophied The four cardiac alves and

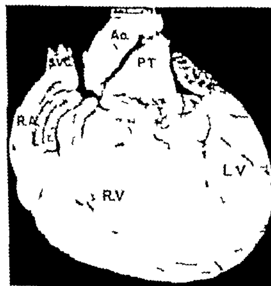


Fig 3 Exterior ew h enlarged heart The entire m ocardium f he righ en le is ered by subepicardial adipose ssue S V C Superior ena ca R A Righ trium R V Righ entricle L A A Lef trial ppend ge L V Lef entricle P T Pulmonary tr k A A ending aorta.

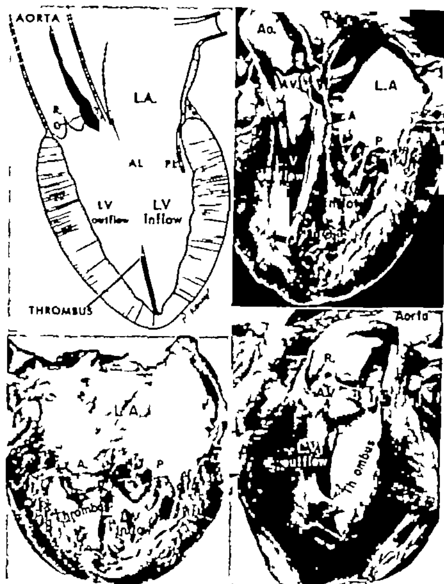


Fig. 4. Opened left ventricle disclosing the fibrin curtain which separated the inflow and outflow tracts. *Upper left.* Diagram depicting the thrombus which was adherent to the anterior posterior and apical walls of the left ventricle and to the ventricular aspect of the anterior leaflet (*A.L.*) of the mitral valve. A strand of the thrombus extends into the ostia of both the right (*R.*) and the left coronary arteries. *P.L.* Posterior mitral leaflet. *A.L.* Anterior mitral leaflet. *L.A.* Left atrium. *Upper right.* View after removal of the anterolateral wall of the left ventricle. *A.* Anterior mitral leaflet. *P.* Posterior mitral leaflet. *Lower left.* Opened left atrium (*L.A.*), mitral valve, and left ventricle. The area demarcated by the dashed line depicts the largest communication between the inflow and outflow tracts. *Lower right.* Opened left ventricle, aortic valve (*A.V.*), and ascending aorta. Again, the area demarcated by the dashed line indicates the largest communication between the divided left ventricle.

the three major coronary arteries were normal. A thrombus measuring 0.4 cm. in thickness was present in the left ventricular cavity extending into the ascending aorta (Fig. 4). This thrombus separated the inflow and outflow tract and was adherent to the left ventricular apex, anterior and posterior walls, and to the ventricular aspect of the anterior mitral leaflet. A fibrin strand from this thrombus extended into the ostia of both the right and the left coronary arteries but these vessels were in no way obstructed. Several foci of endocardial thickening were present in the apical portion of the left ventricle. An adherent, nonobstructing organizing thrombus was present in the superior vena cava. Histologic study of sections of myocardium disclosed generalized hypertrophy of the fibers, and

focal mild to moderate interstitial fibrosis. No inflammatory cells were present in the sections of the cardiac walls.

The vessels in the lungs were quite congested, and multiple pulmonary emboli and infarctions were present. Sections of the liver disclosed massive centrolobular hemorrhage and necrosis.

Comment and summary

In spite of the frequency of intracardiac mural thrombosis in idiopathic cardiomyopathy, left ventricular curtain thrombi have not been described previously. Although hemodynamic studies were not performed during the last few weeks of the patient's life, anatomic observations suggest that the fibrin thrombus may have produced some degree of obstruction between the inflow and outflow tracts of the left ventricle. The history of previous pulmonary and systemic emboli along with an unremitting deteriorating course should have suggested a further anatomic cause for his low-output syndrome. Left ventricular angiography might have led to the premortem diagnosis of the curtain thrombus.

This case is presented to illustrate the entity of curtain thrombus in association with primary myocardial disease. Angiographic recognition of this form of thrombus and its surgical removal could prove to be lifesaving in a patient with this form of intracavitary clot.

REFERENCES

1. Goodwin, J. F., Gordon, H., Hollman, A., and Bishop, M. B.: Clinical aspects of cardiomyopathy, Brit. M. J. 1:69, 1961.
2. Mattingly, T. W.: Clinical features and diagnosis of primary myocardial disease, Mod. Concepts Cardiovas. Dis. 30:677, 1961.
3. Dye, C. L., Rosenbaum, D., Lowe, J. C., Behnke, R. H., and Genovese, P. D.: Primary myocardial disease, Ann. Int. Med. 58:426, 1963.
4. Stuart, K. L., and Hayes, J. A.: A cardiac disorder of unknown aetiology in Jamaica, Quart. J. Med. 32:99, 1963.
5. Massumi, R. A., Rios, J. C., Gooch, A. S., Nutter, D., DeVita, V. T., and Datlow, D. W.: Primary myocardial disease, Circulation 31:19, 1965.
6. Fowler, N. O., and Gueron, M.: Primary myocardial disease, Circulation 32:830, 1965.
7. Segal, J. P., Harvey, W. P., and Gurel, T.: Diagnosis and treatment of primary myocardial disease, Circulation 32:837, 1965.

Clinical pathologic conference

Cecil A. Krakower, M.D.
Norman B. Roberg, M.D.
Edwin J. Liesner, M.D.
Chicago, Ill.

History

The patient was a 56-year-old Mexican housewife. Since she spoke no English her history was obtained through an interpreter. Six months prior to her second and last admission to the Research and Educational Hospitals she was seen in the Outpatient Clinic because of shortness of breath, 2-pillow orthopnea, nonproductive cough, anorexia, frequent nausea and vomiting, and pain in and weakness of her lower extremities. She had had exertional dyspnea and ankle edema for some 2 years prior to being seen in this hospital. In her past history she stated that she had had "heart trouble" at the age of 3. She had otherwise been well, except for appendectomy at the age of 35. She had had 9 children, of whom 5 were alive and well. Examination at the Clinic revealed that the anteroposterior diameter of the chest was increased. Respirations were shallow and rapid (28 per minute). The chest was hyperresonant to percussion. Breath sounds were decreased in intensity. There were rales at the basis of each lung. As for the cardiovascular system, the blood pressure was 140/102 mm. Hg. Peripheral pulses were palpable and thready, equal bilaterally with a rate of 80 per minute. There was distention of the veins of the neck for 3 cm. above the clavicle when the patient was elevated 30 degrees from the supine position. The heart rate was extremely rapid at 148 per minute. S_1 was maximum at the apex, and S_2 at the base. P_2 equaled A_2. There were no murmurs, but the heart sounds were decreased in intensity. The edge of the liver was thought to be 3 cm. below the costal margin. There was no peripheral edema. She was treated with digitalis and mercurials. Two weeks later she was admitted to the hospital because of the continued complaint of pain in the lower extremities and weakness. Her temperature was 100.6°F. Pulse was 76 and grossly irregular. Blood pressure was 120/80 mm. Hg. The heart showed no enlargement by physical examination, although it was considered to be diffusely enlarged on the x-ray film (Fig. 1). The heart sounds were normal. There were no murmurs, no opening snap, and no gallop rhythm. The chest was clear. The abdomen was protuberant. There were no enlarged organs, masses, or tenderness. The extremities were thought to be normal. The neurological examination was within normal limits.

Laboratory data. Hemoglobin 16.. hematocrit 53 white blood count 8,500 with stabs 7, segmented neutrophils 59, lymphocytes 30, monocytes 4. Urinalysis was within normal limits. The electrocardiogram revealed a rate of 62, low voltage in the limb leads, QRS of 0.08 sec., approximate QRS vector in frontal plane +70°, sagging S-T in Leads II, III, aVF, V_{4-6} and atrial fibrillation (Fig. 2). A 2-hour postprandial sugar was 134 mg. Blood urea nitrogen, electrolytes, alkaline phosphatase, uric acid, and transaminase were all within normal limits. The Kahn and Wassermann tests were negative. On the third hospital day she developed an acute arthritis of the knee joint with swelling, tenderness, and warmth. Turbid fluid which showed stringy clot with normal glucose value was aspirated from the joint. The total count was 10,000 white cells. These cells were mostly mononuclears. Cultures of the synovial fluid were negative for gonococci and for tubercle bacilli. A throat culture was negative for beta streptococci. The antistreptolysin-O titer was positive up to dilution of 1,250. C-reactive protein was positive. Preparation for lupus erythematosus and latex fixation test for rheumatoid arthritis were negative. She was treated with salicylates and became promptly asymptomatic. After 17 days in the hospital she was discharged on 0.1 mg. of digitoxin daily. She was followed in the Outpatient Clinic. She failed to take her medication as prescribed. She complained of chest pain brought on by exertion or excitement. This was relieved by nitroglycerin. She also had constant pain in the left ... Six days prior to her second admission she developed a cold with fever, headache, cough productive of greenish sputum and breathlessness. She had some back ache aggravated by breathing and coughing. She complained of nonradiating pain "around the

From the University of Illinois Research and Educational Hospitals, Chicago, Ill.
Received for publication July 14, 1966.
Address: Department of Pathology, University of Illinois Medical Center, 1853 West Polk St., Chicago, Ill. 60612.

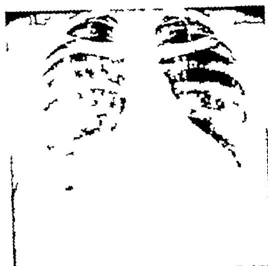


Fig. 1. Posteroanterior view of the chest with the patient in the sitting position showing diffuse cardiac enlargement.

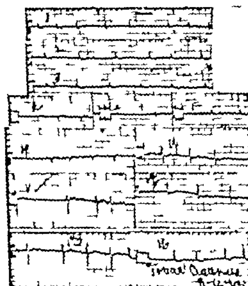


Fig. 2. Electrocardiogram. Rate 61, atrial fibrillation, QRS 0.08 sec, QRS vector +70°. Low voltage in limb leads. S-T sags in Leads II, III, aVF, V4-6. ST-T changes compatible with digitalis effect.

heart. One day prior to admission she became disoriented and was unable to recognize members of her family.

Physical examination. Physical examination revealed delirious semicomatose, slimmy cyanotic tachypneic patient. Temperature was 103.2°F, blood pressure 90/60 mm. Hg, pulse 120, respirations 3... The pupils were dilated and fixed. The fundi showed mild vascular tortuosity with an arteriovenous ratio of 1:3. There were no nicking and no papilledema. Ears, nose, and throat were not remarkable. Thyroid was not enlarged. There was no distention of the neck veins. Examination of the lungs revealed labored expirations. There was no dullness anteriorly but dullness to the right posteriorly. There were diffuse expiratory wheezes and rhonchi with moist rales over both lungs, more marked on the left. The cardiac silhouette was enlarged. The point of maximum impulse was felt 2 cm. outside the mid-clavicular line in the fifth intercostal space. The first and second heart sounds were distant, although S_1 was maximal at the apex. There were no heart murmurs. The rhythm was irregularly irregular with a pulse of 80 at the periphery and 110 at the apex by auscultation. The breasts were free of masses. The abdomen was soft, nontender. No organs or masses were palpable except for the liver, which was 1 fingerbreadth below the right costal margin. One-plus sacral edema was noted. There was no tenderness of the calf or ankle edema. The nail beds were cyanotic. Neurological examination limited by the clouded conscious state of the patient appeared to be within normal limits. Pelvic examination revealed a large rectocele and cystocele.

Laboratory data. Hemoglobin 16.2, hematocrit 52, white blood count 11,350. Differential: 1 progranulocyte, 3 myelocytes, 1 metamyelocyte, 32 stab neutrophils, 34 segmented neutrophils, 17 lymphocytes, 12 monocytes. Three nucleated red blood cells per 100 white blood cells, giant platelets, and 2-plus toxic granulation were noted. Mean corpuscular hemoglobin concentration was 31. Urinalysis: specific gravity 1.016, albumin 2 plus, red blood cells 5 per high-power field, white blood cells 9 per high-power field, few hyaline granular casts. Blood urea nitrogen was 43, sodium 128, potassium 5.3, chloride 88, carbon-dioxide combining power 26 milliequivalents per liter. The carbon-dioxide content of arterial blood was 51.39 volumes per cent, oxygen saturation was 89 per cent, and pH was 7.28. Serum glutamic oxalacetic transaminase 124. Sputum culture man *Hemophilus* *influenzae*, few *Proteus mirabilis* and *Candida albicans*. Cultures of blood, urine, and spinal fluid were sterile. ECG: rate about 120, atrial fibrillation, QRS of 0.08 sec., QRS vector in frontal plane +70°, nonspecific ST-T changes. The chest x-ray film revealed an ill-defined infiltrate in the lower lobe and partially in the upper lobe, of the right lung. There was cardiomegaly.

Hospital course. The patient had considerable respiratory distress. She was unable to cough up the tracheobronchial secretions and required tracheal suction. A tracheostomy was performed, but the patient failed to improve. Treatment included antibiotics (tetracycline, streptomycin), supplementary intravenous fluids, and oxygen with intermittent positive-pressure breathing apparatus. She died 3 days after admission.

Discussion

DR. ROBERG: The differential diagnosis is complicated by the facts that the patient

was 56 years old and spoke no English. The probability of two or more coexistent diseases increases with age, and the linguistic barrier interferes with a clear impression of the nature and severity of the pains in and weakness of the legs as well as the differentiation between the factors of cardiac and pulmonary insufficiency. Several observations suggest long-standing obstructive pulmonary insufficiency: the increased anteroposterior diameter of the chest and the hyperresonance with diminished breath sounds. There is little evidence of congestive heart failure: there was no peripheral edema, the neck veins filled for only 3 cm. with the patient lying at an angle of 30 degrees, and the edge of the liver was only 3 cm. below the costal margin. This could represent mild enlargement on the basis of circulatory congestion or the low position of a normal-sized liver which is pushed down by the low diaphragm associated with emphysema.

The central problem is the nature of the heart disease and the relationship of the heart disease to the pulmonary insufficiency, the symptoms and signs in the legs, and the later abnormalities of the sensorium, kidneys, and peripheral blood. The description of the heart is not distinctive: it was enlarged diffusely, and no murmurs were heard. The atrial fibrillation implies atrial disease, and the normal electrical axis of the ECG suggests that there was no preponderant hypertrophy of the left ventricle. We may assume that the physicians in the Outpatient Clinic did not consider that any significant heart failure was present, inasmuch as she was not admitted to the hospital, and ambulatory treatment with digitalis and diuretics was started.

The patient was admitted to the hospital 2 weeks later because of pain in and weakness of the legs and not because of heart failure: there was no shortness of breath, edema, or hepatomegaly; the lungs were clear both upon physical and x-ray examination. The heart was grossly enlarged, atrial fibrillation was still present, and the rate was recorded at 62 and 76 per minute. Neither murmurs nor a gallop rhythm was present. The urine was normal, as were several standard laboratory tests. The hemoglobin of 16.2 Gm. and the hematocrit of 53 per cent are high for a chronically ill woman of 56 and suggest mild polycythemia secondary to pulmonary insufficiency.

On the third hospital day the patient developed an acute nonbacterial inflammation of the knee which responded promptly to treatment with salicylates. This is highly suggestive of an hyperergic inflammation, and the antistreptolysin titer of 1:250 indicates a streptococcal infection within recent weeks or months. No lupus erythematosus cells were found, and the latex fixation test was negative. As Adatto[1] has emphasized recently, rheumatic fever does occur in the older age groups, but there is no evidence that our patient had rheumatic heart disease or that the weakness of the legs and the pain were consistent with rheumatic fever.

The patient left the hospital after 17 days, taking a maintenance dose of digitoxin, and was followed in the Outpatient Clinic for the next 5 months. During these 5 months she complained of chest pain consistent with angina pectoris. It was precipitated by exertion and excitement and was relieved by nitroglycerin. She also had during this time constant pain in the left ankle. Constant monoarticular arthralgia for 5 months is rare in such pathergic inflammations as rheumatic fever, rheumatoid arthritis, and lupus erythematosus.

Six days before her second admission to the hospital, and 9 days before her death, the patient suffered the onset of fever, headache, cough with greenish sputum, backache aggravated by breathing and coughing—which may have represented pleurisy—and increased shortness of breath. When admitted to the hospital, she was comatose, delirious, cyanotic, and in respiratory distress. Her skin was clammy, the blood pressure was 90/60 mm. Hg, the pulse was 120, and the temperature was 103.2°F. This clinical description, with the pulmonary findings, is consistent with the severe hypoxia which occurs when an acute bronchitis or pneumonitis is superimposed upon chronic pulmonary insufficiency. Except for slight sacral edema, there was no evidence of congestive heart failure. The urine was abnormal for the first time, showing small amounts of albumin and a few red and white cells and hyaline casts. The renal abnormality, as well as the mental depression, could have been related to dif-

fuse vascular disease but more likely were due to the peripheral circulatory failure and hypoxia. The elevated white blood cell count is consistent with the pulmonary infection and we see again the relative polycythemia which I choose to relate to her chronic pulmonary insufficiency. The marked shift to the left of the leukocytes, the normoblasts, and the giant platelets is found in the myelophthisic anemias—and sometimes there is moderate polycythemia rather than anemia—associated with dissemination of carcinoma or tuberculosis to the bone marrow. This raises the possibility that our patient might be suffering from such a disseminated disease involving the lungs, heart, and pericardium. Inasmuch as the bone marrow can respond similarly to the hypoxia of severe heart failure, it is more probable and more consistent with unity of diagnosis to invoke hypoxia as the cause of the hematologic picture. Thus, we may ascribe the renal, cerebral, and hematologic changes to hypoxia, and also the elevation of the SGOT to 124 to passive congestion and hypoxia of the central aspect of the hepatic lobules, rather than to myocardial infarction, despite the history of chest pain. The arterial blood oxygen saturation of 89 per cent can be due either to a defect in diffusion or to arteriovenous shunting, or to both. The arterial CO_2 content of 51.6 volumes per cent corresponds to, at the pH of 7.28, an arterial pCO_2 of 59 mm. Hg (normal 40 mm. Hg) and indicates defective alveolar ventilation, which is consistent with chronic bronchopulmonary disease.

The ill-defined infiltrates in the upper and lower areas of the right lung may be either pneumonitis or pulmonary infarction; pulmonary infarction occurs preponderantly in the lower lobes, whereas lesions of the upper lobes are usually of infectious origin.

The patient died an asphyxial death. During the last 3 days she could not clear her tracheobronchial secretions, and suction, tracheostomy, intermittent positive pressure assisted breathing, and antibiotics did not relieve the ventilatory impairment. During the terminal illness there was no abnormal distention of the cervical veins, enlargement of the liver, or edema. There is, therefore, no basis for invoking heart failure on the basis of myocardial insufficiency, cardiac tamponade, or pulmonary embolization.

In summary, there was evidence of disease of three systems. (1) The heart was enlarged generally without evidence of left ventricular hypertrophy. There were no murmurs; the history suggests angina pectoris, and congestive heart failure was mild and easily controlled. (2) The lungs seem to have been the seat of obstructive emphysema and chronic bronchitis, and the terminal illness was probably infectious, with the possibility of pulmonary infarction. (3) Throughout the 6-month illness there was pain in and weakness of the legs. There was persistent pain in the left ankle and an episode of acute, nonbacterial arthritis of a knee which responded promptly to salicylates. We are not told of any sensory or motor defects in the legs. During the terminal illness there was also impairment of the bone marrow, brain, and kidney, which was probably hypoxic but could represent intrinsic disease.

Can we adhere to the principle of unity of diagnosis and explain all of the patient's signs and symptoms—leaving aside the chronic bronchopulmonary disease—on the basis of a single disease? There are three classic approaches to differential diagnosis based on the unity of diagnosis: (1) to postulate a focal disease which has metastasized to other organs, (2) to seek a disease process affecting particularly an anatomic system, such as the reticuloendothelioses or primary amyloidosis, which may affect many anatomic sites, or (3) to assume a single disease, such as sarcoidosis, which may affect several organs. If only the first two categories are considered, there is insufficient evidence for focal disease with metastasis such as tuberculosis or carcinoma. Either of these diseases, when disseminated, can cause rapidly progressive pulmonary insufficiency, restrictive cardiac insufficiency, and myelophthisis. However, neither of them would explain the weakness and pain in the legs, the six months of monoarticular arthralgia, and the acute brief inflammation of the knee. Under the second category, that of systemic diseases affecting many organs, there is only one group of diseases which requires serious consideration, the group characterized by a hyperergic and pathergic reaction of con-

nective tissue This category is broad and we need consider only rheumatic fever periarteritis nodosa granulomatous arteritis, and systemic sclerosis (scleroderma)

Rheumatic fever does occur in older persons and the acute nonbacterial arthritis of the knee which responded promptly to salicylates and was associated with a high antistreptolysin titer would be consistent with rheumatic fever The chronic pain in one ankle and the weakness of and pains in the legs are not suggestive of rheumatic fever The descriptions of the heart do not suggest any specific diagnosis it was generally enlarged there were no murmurs or third heart sound the atrial fibrillation implies atrial disease and the normal electrical axis suggests that there was no preponderant left ventricular hypertrophy Thus, there is no specific evidence of rheumatic heart disease The mild and intermittent elevations of venous pressure speak against any of th forms of restrictive heart disease which can be caused by fibrosis or infiltration of the pericardium epicardium myocardium or endocardium Systemic sclerosis (scleroderma) could indeed cause this nondescript picture of heart disease could cause or aggravate the pulmonary insufficiency and could cause a peripheral neuropathy of the legs. There are no other manifestations of systemic sclerosis, however and the arthritis remains unexplained Systemic lupus erythematosus, similarly is only partly consistent with this illness.

I cannot advance any specific diagnosis with conviction and my diagnosis is based more upon sentiment than upon clinical evidence just a century ago Kussmaul and Maier published their classic description of periarteritis nodosa Their description of a previously undescribed characteristic arterial disease (Periarteritis Nodosa) which is ushered in by Bright's disease and a rapidly progressive generalized muscular paralysis is not the syndrome shown by our patient. Our patient's illness is more consistent with a variation of periarteritis described by Rose and Spencer[4] a variation which might be classified better as a form of granulomatous arteritis. The patients of Rose and Spencer had severe granulomatous arteritis of the lungs, and twice the frequency of cardiac involvement as in classic periarteritis nodosa and the kidney which was involved only late in the disease, showed glomerulitis. Some of these patients had an elevated antistreptolysin-O titer and the authors believed that there was some association of this arteritis with rheumatic fever and rheumatoid arthritis. I wish to postulate that our patient suffered from a similar form of hyperergic vasculitis superimposed upon chronic bronchitis and emphysema with involvement of the lungs, myocardium and kidneys, and the joints muscles, and nerves of the legs.

DR. LIEBNER The posteroanterior film of the chest on the first admission was a portable one taken with the patient in the sitting position This would have tended to limit somewhat the patient's deep inspiratory effort and may have increased the transverse diameter of the heart The film showed poor aeration of the lower lung fields and an increase in the size of the cardiac silhouette The cardiomegaly suggested diffuse myocardial enlargement The aorta was not particularly dilated. From the lateral films that were available it was difficult to determine whether there was any significant enlargement of the left atrium There were no studies with barium to help in this respect The hilar vasculature of the posteroanterior film was not prominent

The last two portable films of the chest were taken during the second admission. The earlier film showed an increase in density extending from the lower portion of the right hilum and obscuring the border of the right side of the heart. The vascular pattern appeared to be accentuated throughout the lung fields. The later film showed a slight reduction in size of the above mentioned density A pulmonary infarct could easily explain these findings. However pneumonic consolidation or congestive changes resulting from myocardial failure could underlie this density as well

Films of the feet, ankles, and knees showed no destruction of cartilage or narrowing of the joint spaces. There was irregular spurring of the tibial aspect of the knee joints, more marked on the right than on the left side These findings were more in keeping with degenerative changes than with rheumatoid arthritis. Alterations in the soft tissues about the joints could not be

evaluated since the films were taken to demonstrate osseous detail

DR. KRAKOWER There was no peripheral edema, neither were there any pleural or peritoneal serous effusions at postmortem examination. There was 25 ml of slightly turbid fluid in the pericardial sac, but no pericardial adhesions. The heart was moderately enlarged weighing 400 grams (normal 250 to 350 grams) The epicardium was smooth with a goodly amount of fat The right atrium was somewhat enlarged Its endocardial surfaces were not remarkable. The fossa ovalis was closed There was fusion of the cusps of the tricuspid valve The leaflets however were thin with no shortening but with some granularity of contact points. Some of the chordae attached to the valve were thickened but not appreciably shortened The circumference of the valve was 11.5 cm. (normal 12.0 cm) There was some enlargement of the right ventricle The thickness of its myocardium was at the upper limit of normal at 0.3 cm. The thickening was perhaps a little better reflected in the trabeculae carneae and papillary muscles of the ventricle The pulmonary valve was within normal limits. Its circumference was 7.0 cm (normal 8.5 cm) There were no atherosclerotic changes in the pulmonary artery or its branches. The left atrium was greatly enlarged with despite this, myocardial hypertrophy The endocardium was thickened particularly posteriorly and near the orifice of the appendage there was an organizing mural thrombus, 2.0 by 3.0 cm The orifice of the mitral valve was narrow and of fish-mouth type (Fig 3) The leaflets were fused and thickened There was, however no appreciable calcification and the cusps were pliable The chordae were thickened and shortened There were minute endothelial-covered granules at the line of closure of the valve The circumference of the mitral valve was 5.5 cm (normal 10 cm) The left ventricle was not increased in size Its endocardium was normal Its myocardium measured 1.3 cm (normal 0.8 to 1.0 cm.) in thickness. It was red-brown in color with no evidence of infarction or gross fibrosis. The aortic valve presented thin cusps, with no adhesions and measured 6.5 cm in circumference (normal 7.5 cm) The aorta presented minimal sclerosis. The coronary



Fig 3 View of the enlarged left atrium with fish mouth mitral orifice and with a mural thrombus to the left of the mitral valve near the opened atrial appendage.

arteries were normally distributed of good caliber with some atheroma The lungs were at the upper limits of normal weight (right 520 grams left 430 grams) There were pleural and interlobar adhesions There was generalized vesicular emphysema The whole of the tracheobronchial tree was filled with mucopurulent exudate and its mucosal surfaces were reddened In the medial portion of the right middle lobe the bronchi were decreased in caliber with ectasis beyond the constricted portions. These latter were filled with mucopurulent exudate In addition this portion of lung was airless and fibrotic in appearance Elsewhere the lungs on section revealed pinpoint exudate in the distal ramifications of the bronchi associated in areas with infiltrates about them There were thromboemboli in branches of the pulmonary artery to the right upper lobe but no infarction of the lung The peribronchial and paratracheal lymph nodes were enlarged soft reddish gray with no apparent granulomata. The liver weighed 1,270 grams (normal 1,500 grams) It was firm



Fig. 4 Microscopic view of the myocardium with a resolving Aschoff body

with congestive and fatty changes. The spleen weighed 160 grams (normal 150 to 200 grams) Its capsule was thickened It was a firm spleen with a reticulated pattern on section no clearly defined follicles, but with an old healed infarct less than 1 cm in maximal diameter The kidneys each weighing 190 grams (normal 150 grams) were congested and presented an old infarct in each The other organs were not remarkable except for a hydrosalpinx on the left with associated ovarian adhesions

Microscopically sections through the left ventricle revealed hypertrophy of the muscle fibers and wide fibrosed perivascular spaces. In most instances these showed elongated polarized fibrocytes with a fibrillar collagenous framework Furthermore in many areas there were resolving Aschoff nodules lacking fibrinoid changes but presenting the characteristic arrangement and quality of cells seen in Aschoff lesions (Fig 4) The thrombus in the left atrium was a bland one and was undergoing organization associated with a nonspecific chronic inflammatory response. There were no underlying Aschoff lesions. The mitral valve was quite highly vascularized and fibrosed In the lungs there appeared to be two processes aside from chronic passive congestion and emphysema. There was an older process as represented in the right middle lobe with bronchostenosis, bronchiectasis and bronchiolectasis associated with extensive fibrosis. Also elsewhere there was considerable lymphocytic infiltration of the walls of the bronchi and bronchioles with hyperplastic and metaplastic epithelial changes in instances. There was also a recent process in which mucopurulent exudate filled and distended bronchi and bronchioles. Some of the latter showed early organization with fibroblastic proliferation Commonly there was spread of the inflammatory exudate from the bronchioles to the adjacent alveolar ducts and alveoli The exudate was made up of fibrin and polymorphonuclears. In one area there was a more extensive pneumonic process with hyaline-like deposits on the walls of alveoli and with serous exudate as well as a variety of inflammatory cells in the lumens. In the liver there was some fatty change but principally there were changes of chronic passive congestion, with centrolobular fibrosis and mural fibrous thickening of the branches of the hepatic veins. The other organs revealed

changes secondary to chronic passive congestion. In the bone marrow there was a shift of the hematopoietic elements to the left with retarded maturation of the white and red blood cell series.

This is another example of clinically silent advanced rheumatic heart disease with mitral stenosis. Of interest too is the fact that at the age of 56 this woman had recently had another attack of acute rheumatic fever as indicated by the resolving Aschoff lesions in the myocardium. Needless to say this patient's pulmonary disease helped to obscure the detection and nature of the heart condition. She had rather advanced diffuse chronic bronchitis and emphysema with bronchiostenosis and bronchiectasis of the right middle lobe. Death was due to superimposed widespread acute bronchitis bronchiolitis, and bronchopneumonia, with pulmonary embolism to the right upper lobe.

Diagnosis. Rheumatic heart disease with mild tricuspid stenosis marked mitral stenosis, and with superimposed resolving acute rheumatic myocardial lesions. Marked chronic bronchitis and pulmonary emphysema with superimposed acute bronchitis bronchiolitis, and bronchopneumonia.

REFERENCES

1. Adatto, I. J. et al. Rheumatic fever in the adult, J.A.M.A. 194:1043, 1965.
2. Kussmaul, A., and Maier R. Über eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis Nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. 1:484-518 (Feb. 1) 1866.
3. Rose G. A., and Spencer H. Periarteritis nodosa, Quart. J. Med. 26:43 1957.

Cor pulmonale in children: Review and etiological classification

*Anne D. Morgan, M.D.**
Gainesville, Fla.

The term "cor pulmonale" is frequently misused and misunderstood. It comes from the Latin words *cor*, meaning heart, and *pulmo*, meaning lung. In a strict sense, cor pulmonale refers to hypertrophy and failure of the right ventricle resulting from a primary lung disease. In a more liberal sense, the term may be used to describe an increased work load on the right ventricle from alterations in the pulmonary circulation which may result from (1) diseases primarily affecting pulmonary ventilation and respiratory function, (2) diseases primarily affecting the pulmonary vasculature, or (3) primary cardiac diseases producing secondary alterations of the pulmonary vasculature.

There has been much debate about a satisfactory definition for the term "cor pulmonale" or "chronic cor pulmonale," but at a meeting of the World Health Organization in 1963, it was decided to exclude primary cardiac diseases and define chronic cor pulmonale as ". . . hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or of congenital heart disease." Thus, the term should include right ventricular hypertrophy resulting from any type of abnormality of respiratory structure and/or function.

Cor pulmonale has received little attention in children. It is being recognized with increasing frequency, however, because of improved diagnostic methods and treatment. Many conditions which previously caused death from an acute respiratory infection in an early stage may now progress to the development of chronic lung disease. A classification of the etiological causes of cor pulmonale is of more than academic interest because an understanding of the natural history and basic pathophysiology of the underlying respiratory disorder is essential for successful therapy. There is no recent physiologic or pathologic survey of cor pulmonale in children. Therefore, this paper is a review and proposal of an etiological classification of cor pulmonale in children based on the primary pathophysiology.

Mechanisms in pathogenesis

Two basic mechanisms are involved in the pathogenesis of cor pulmonale. The first is alveolar hypoventilation, which

From the Department of Pediatrics, University of Florida College of Medicine, Gainesville, Fla.
Supported in part by a Developmental Physiology Training Grant (T1-HD 54), a Cardiovascular Training Grant (5T -HE 5493-04) (S1) (trainee Dr. Morgan), and the Florida Heart Association.
Received for publication Nov. 14, 1966.

*Presently Assistant Chief of Pediatrics, National Jewish Hospital at Denver, and Senior Instructor in Pediatrics, University of Colorado Medical Center, Denver, Colo. Address: National Jewish Hospital at Denver, 3800 East Colfax Ave., Denver, Colo., 80206.

may be caused by primary parenchymal lung diseases or initiated by conditions outside the lungs. The second is an anatomic reduction of the pulmonary vascular bed resulting from diseases primarily affecting the pulmonary vessels either by intraluminal obstruction or extraluminal occlusion and/or obliteration.

Cor pulmonale which results primarily from alveolar hypoventilation is sometimes called "hypoxic" cor pulmonale and that which results primarily from pulmonary vascular disease is called "hypertensive" cor pulmonale. This terminology however seems to be poor in that *all* causes of cor pulmonale eventually result in some degree of hypoxemia and pulmonary hypertension. In many conditions the extent to which both basic mechanisms are operative in the genesis of pulmonary hypertension has not been clearly elucidated. Nevertheless, an attempt has been made to classify the etiological causes of cor pulmonale in children according to which basic mechanism appears to be of primary importance in the pathogenesis, namely, alveolar hypoventilation or pulmonary vascular disease (Tables I and II).

The common feature in all cases of cor pulmonale is an over-all reduction of the total pulmonary vascular bed with an increased resistance to pulmonary blood flow and a variable degree of pulmonary hypertension. The extent of structural changes in the lungs and pulmonary vessels is variable depending on the type of underlying pulmonary disease. The factors responsible for restriction of the pulmonary vascular bed are mechanical (obliterative and obstructive vascular disease) and/or functional (vasoconstriction due to re-

Table I. Etiological classification of cor pulmonale in children

Cor pulmonale due to alveolar hypoventilation
- A. Alveolar hypoventilation from primary lung disease
  - 1. Obstructive lung disease
    - a. Cystic fibrosis
    - b. Bronchiolitis
    - c. Bronchial asthma
    - d. Emphysema
    - e. Chronic obstruction of upper airs
    - f. Bronchiectasis
  - 2. Restrictive lung disease
    - a. Diffuse interstitial fibrosis (Hamman-Rich syndrome)
    - b. Wilson-Mikity syndrome
    - c. Chronic pneumonitis
    - d. Tuberculosis
    - e. Idiopathic pulmonary hemosiderosis
    - f. Bronchiectasis
- B. Alveolar hypoventilation from extrinsic conditions
  - 1. Neuromuscular disease
    - a. Polio
    - b. Guillain-Barré syndrome
    - c. Muscular dystrophy
    - d. Myasthenia gravis
    - e. Amyotrophic lateral sclerosis
  - 2. Thoracic cage deformity
    - a. Kyphoscoliosis
    - b. Pectus excavatum and pectus carinatum
    - c. Spondylitis
    - d. Thoracoplasty
  - 3. Respiratory muscle weakness associated with metabolic or endocrine diseases
  - 4. Respiratory syndrome of obesity (Pickwickian)
  - 5. Congenital anomalies
    - a. Diaphragmatic hernia
  - 6. Respiratory center depression
    - a. Drugs, anesthesia
    - b. Central nervous system disease
    - c. High altitude

Table II. Etiological classification of cor pulmonale in children (continued)

Cor pulmonale due to pulmonary vascular disease
- A. Intraluminal obstruction
  - 1. Reactive pulmonary artery vasoconstriction
    - a. Absent pulmonary artery
    - b. Altitude
  - 2. Thromboembolism
    - a. Sickle cell anemia
    - b. Rheumatic fever
    - c. Subacute bacterial endocarditis
    - d. Schistosomiasis
    - e. Ventriculojugular shunt
    - f. Carcinomatosis
  - 3. Primary pulmonary hypertension
- B. Extraluminal occlusion and/or obliteration
  - 1. Alveolocapillary block
    - a. Sarcoidosis
    - b. Collagen diseases
      - (1) Rheumatoid arthritis
      - (2) Disseminated lupus erythematosus
      - (3) Scleroderma
      - (4) Dermatomyositis
    - c. Pulmonary alveolar proteinosis

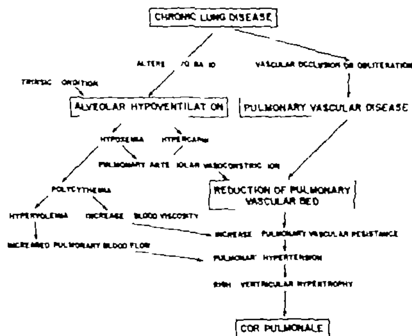


Fig. 1. Mechanisms involved in the pathogenesis of cor pulmonale.

gional and generalized alveolar hypoventilation with its resultant arterial hypoxemia and hypercapnia) (Fig. 1).

Alveolar ventilation is primarily controlled by the medullary respiratory centers. Studies suggest that the medullary CO_2 chemoreceptor is located within or just beneath the pia on the ventrolateral surface of the medulla and that the hydrogen ion concentration of the cerebrospinal fluid is the major factor governing its response.[4] Alveolar ventilation can be affected by lesions or depression at the medullary level, altered neuromuscular transmission from it, or impairment of respiratory muscle function. At the end organ both obstructive and restrictive lung disease can produce alveolar hypoventilation by causing an increase in airway resistance and/or a decrease in lung compliance, both of which result in an increased work of breathing and disturbances in ventilation perfusion relationships.

Alveolar hypoventilation results in arterial hypoxemia and hypercapnia. Both hypoxemia and hypercapnia produce pulmonary vasoconstriction and can be closely correlated with pulmonary arterial pressure.[5] Vasoconstriction produced by hypoxia has been shown to occur predominantly at the precapillary level since pulmonary capillary "wedge" and left atrial pressures remain normal whereas there is a marked rise in pulmonary arteriolar resistance and pulmonary arterial pressure.[7] The mechanism by which these changes are initiated is not fully understood, but there appears to be an interaction between hydrogen ion concentration and hypoxia on pulmonary vascular smooth muscle, and changes in pH markedly influence any intrinsic pulmonary vascular changes that are responses to local O_2 tension.[8,9] The influence of hydrogen ion concentration on the pulmonary vasoconstrictive response to hypoxia in patients with chronic lung disease was demonstrated by Enson and associates.[8] They showed that at a low [H+] (high pH) severe hypoxia was not associated with a significant pressor response in the pulmonary artery but at a high [H+] (low pH) pulmonary arterial pressure was extremely sensitive to hypoxia. Recently Vogel and Blount also showed that hydrogen ion concentration plays a dominant role in the regulation of pulmonary arterial pressure; an increase in hydrogen ion concentration is associated with an increase in pulmonary hypertension and correction

of the acidosis causes a decrease in pulmonary arterial pressure.

Another important hemodynamic alteration produced by arterial hypoxemia is the development of a secondary polycythemia which is associated with an increase in blood volume (hypervolemia) and an increase in blood viscosity.[9] Increased blood volume, by increasing venous return to the right heart and increasing pulmonary blood flow will further elevate pulmonary arterial pressure in the face of a restricted pulmonary vascular bed. Increased blood viscosity will tend to increase pulmonary vascular resistance and thus aggravate pulmonary hypertension. The important role of hypoxemia in initiating these hemodynamic disturbances associated with cor pulmonale is indicated by the fact that these circulatory changes may disappear when the hypoxemia has been corrected.[13]

Cor pulmonale secondary to primarily pulmonary vascular disease can result from intraluminal obstruction (multiple pulmonary embolism or primary pulmonary hypertension) or from extraluminal occlusion and obliteration from conditions causing destruction of the pulmonary capillary bed. The latter are almost always associated with diffuse interstitial fibrosis. Hypoxemia therefore results not only from impairment of diffusion caused by destruction of alveolar walls and pulmonary capillaries, but also from disturbed ventilation-perfusion relationships, with obstruction to alveolar ventilation in areas of the lung which are still perfused with blood. It is believed that the latter physiologic disturbance in pulmonary function is probably of greater significance in most situations, even in the rare case of diffusion block.[13]

Although a close correlation has been shown between hypoxia and pulmonary arterial pressure, there appears to be no significant correlation between arterial oxygen saturation and cardiac output.[13, 6] Until recently it was accepted that hypoxic cor pulmonale was associated with a high cardiac output, but it is obvious that the level of cardiac output depends upon numerous complexly interrelated factors including changes in arterial blood gases (hypoxemia and hypercapnia), acid-base balance (acidosis), hypervolemia, anatomic state of the pulmonary vascular bed, and myocardial reserve.[7] These factors are present to different degrees during various stages of a given disease process, and high, normal, or low levels of cardiac output may be found in patients with hypoxic cor pulmonale. In a study of patients with chronic irreversible obstructive lung disease, both at rest and during exercise, Shaw and associates[14] showed that there was no relationship between the arteriovenous oxygen difference and pulmonary arterial pressure. Cardiac output tended to be normal in severely hypoxic patients (O_2 saturation < 85 per cent) and was often abnormally low in less hypoxic patients. On the other hand, when cor pulmonale results from primarily pulmonary vascular diseases, cardiac output is characteristically low and does not increase normally in response to a given exercise load.

In chronic lung disease, cor pulmonale usually does not develop unless there is severe hypoxemia and usually some degree of hypercapnia. In studies of adult patients with emphysema, it has been shown that the arterial O_2 tension is significantly lower and the CO_2 tension higher in patients with cor pulmonale than in those who remain compensated. In most patients with restrictive or obstructive lung disease, potentially reversible functional factors (hypoxemia and acidemia) appear to be responsible for initiating an increase in pulmonary vascular resistance and pulmonary hypertension rather than permanent anatomic lesions, which play a secondary role.[11, 15]

Regardless of all the etiological factors which may produce alterations of blood flow and resistance in the pulmonary circuit, the end result is an elevation of pulmonary arterial pressure which imposes an excessive work load on the right heart and its eventual hypertrophy and failure. The following is a brief discussion of various causes of this situation which can be found in children. It does not include primary cardiac conditions which may alter the pulmonary circulation and thus affect the right heart, but only those conditions responsible for cor pulmonale as defined by the World Health Organization.

Etiological entities

I. Alveolar hypoventilation

A. ALVEOLAR HYPOVENTILATION FROM PRIMARY LUNG DISEASE

1. Obstructive Lung Disease. Hypoxia is believed to be the major factor initiating pulmonary hypertension in conditions that cause chronic obstructive pulmonary disease. Cystic fibrosis is the most common cause in children.[22,23] Alveolar hypoventilation is caused by obstruction of the bronchioles by excessive thick and tenacious secretions. Maldistribution between air and blood flow appears to be the predominant cause of hypoxemia and hypoxemia (and/or acidemia) is the major factor leading to the development of pulmonary hypertension and cor pulmonale in cystic fibrosis.[24] Hypoxemia may be perpetuated by recurrent infections that lead to progressive bronchiectatic changes, but destructive emphysema is not a significant feature of cystic fibrosis.[25] Moss and associates[25] found that cor pulmonale was present in most patients with cystic fibrosis in whom the vital capacity was less than 60 per cent of predicted normal but other workers showed that pulmonary function tests failed to distinguish between patients with pulmonary hypertension and those with normal pulmonary arterial pressure and that the level of pulmonary arterial pressure was directly related to the degree of hypoxemia. In many patients, pulmonary hypertension is reversible by correction of the hypoxemia.[23]

There is considerable controversy about the occurrence of congestive failure in infants with acute diffuse bronchiolitis, but it is potentially a cause of hypoxic cor pulmonale.[23] The diffuse inflammatory reaction associated with intensive bronchospasm results in marked interference with ventilation and gas exchange and autopsy reveals that the lungs are emphysematous, with patchy areas of atelectasis, and the bronchioles are occluded by inflammatory cells.[27] Reynolds[28] found severe hypoxemia in 12 infants with bronchiolitis, and associated hypercapnia in 6.

Most children with bronchial asthma have benign reversible pulmonary changes and cor pulmonale is not likely to occur unless hypoxemia with retention of carbon dioxide from severe alveolar hypoventilation has become chronic. In a review of deaths from asthma in children, Richards and Patrick[29] found only minimal changes in the lung and no evidence of destructive emphysema in most patients, but right ventricular hypertrophy was present in 2 children, indicating that there must have been an excessive work load on the right heart. Griffin and associates[30] reported on 3 children with bronchial asthma in whom pulmonary hypertension was confirmed by cardiac catheterization and autopsy in one child revealed right ventricular hypertrophy, pulmonary atherosclerosis, chronic passive congestion in the lungs and organized thrombi in the small pulmonary arteries.

Emphysematous changes frequently complicate other pulmonary diseases in children and contribute to the development of cor pulmonale. Congenital or infantile lobar emphysema, which can produce severe respiratory distress in the first few days of life, may lead to death from cardiorespiratory failure if it is unrecognized.[31]

A recently recognized cause of "hypoxic" cor pulmonale in children is chronic obstruction of the upper airways.[32-34] The most common etiological cause of obstruction is hypertrophy of tonsillar and adenoid tissue, but there are many other potential causes. Laryngotracheomalacia has been reported to cause cor pulmonale in a 29-month-old child.[35] A congenital tracheal web caused cor pulmonale in a 22-month-old infant.[36] Recognition of these etiological causes of cor pulmonale is of extreme importance since they are potentially correctable and the cardiopulmonary changes are completely reversible.

Bronchiectasis may affect pulmonary function in many ways, producing both obstructive airway disease and restrictive lung disease. Bronchiectasis in children may either be primary or complicate other pulmonary diseases, especially cystic fibrosis. It is part of Kartagener's syndrome (situs inversus, sinusitis, and bronchiectasis).[38] It may also result from repeated respiratory infections in patients with immune globulin deficiency and apparently it may be precipitated by other

causes such as pneumonia measles pertussis endobronchial tuberculosis, or aspiration.[17]

2 Restrictive Lung Disease The most common restrictive lung disease producing cor pulmonale in children is diffuse interstitial fibrosis of unknown etiology (Hamman Rich syndrome)[18,19] The clinical picture is characterized by progressive respiratory insufficiency which may take either an acute or a chronic form. Pathologically there is diffuse interstitial fibrosis reduction of the pulmonary capillary bed and thickening of the alveolar walls. Arterial hypoxemia results from both impairment of diffusion (alveolocapillary block) and abnormal ventilation perfusion ratios caused by replacement fibrosis. Regional hypoventilation results from the fact that the more normally distensible lung units are ventilated preferentially instead of the stiffer regions of the lung

The pulmonary syndrome of Wilson and Mikity has recently been reported in premature infants[20] Although rare, it is a cause of cor pulmonale which will probably be diagnosed more frequently in the future Pathologically the lungs show areas of immaturity with thickening of the alveolar walls and severe cystic emphysema Physiologically the condition resembles the Hamman Rich syndrome and the rare condition of familial fibrocystic pulmonary dysplasia. It is postulated to be a disorder of postnatal alveolar development related to premature birth and the functional use of an immature lung

Chronic pneumonitis with fibrosis and subsequent restriction of the pulmonary vascular bed initiating cor pulmonale in children can be precipitated by bronchopneumonia and lung abscess[21] giant cell pneumonia[22] lipoid pneumonia after oral or nasal administration of drops or sprays containing mineral oil[23] or accidental ingestion of kerosene[24] It may also follow many common viral illnesses in children (influenza, measles, atypical pneumonia psittacosis, giant cell pneumonia, cytomegalic inclusion disease etc) hypersensitivity reactions (to sulfa drugs hexamethonium etc) collagen diseases, uremic pneumonitis radiation pneumonitis, chemicals (war gases beryllium etc) toxoplasmosis histoplasmosis Q fever scrub typhus, and pertussis.

The incidence of cardiopulmonary failure from tuberculosis is said to be increasing in the face of a decreasing mortality rate from this disease[25] The decreased mortality is attributed to improved treatment which results in clinically healed tuberculosis, but persistent tissue defects with extensive fibrosis of the lungs and or pleura may be irreversible causing abnormal ventilation perfusion relationships as well as anatomic restriction of the pulmonary vascular bed.

Although rare another restrictive lung disease seen in children is idiopathic pulmonary hemosiderosis.[26,27] This condition is characterized by repeated episodes of pulmonary hemorrhage resulting in hemosiderosis and diffuse interstitial fibrosis. Pathologically there is degeneration of the alveolar interstitial and vascular elastic fibers, with dilatation and subendothelial sclerosis of the pulmonary vessels.[28] Siderophages may be found in the sputum and hemosiderin in the pulmonary parenchyma can be demonstrated by lung biopsy The etiology is unknown. The disease is usually slowly progressive with death from hemoptysis or chronic cor pulmonale.

B ALVEOLAR HYPOVENTILATION FROM EXTRINSIC CAUSES

1 Neuromuscular Diseases These are the most common extrinsic causes of cor pulmonale from alveolar hypoventilation[29] By affecting peripheral nerves to the respiratory muscles (Guillain Barré syndrome) transmission across the myoneural junction (myasthenia gravis) upper motor neuron cells (amyotrophic lateral sclerosis) lower motor neuron cell (polio) or the respiratory muscles (muscular dystrophy) alveolar ventilation is inadequate and the resultant hypoxemia and hypercapnia initiate pulmonary hypertension

2 Deformities of the Thoracic Cage Such deformities must be severe in order to result in respiratory insufficiency and cor pulmonale during childhood Kyphoscoliosis is the most common thoracic deformity producing cardiopulmonary changes but the condition is usually slowly progressive with the average age of death from cor pulmonale reported to

arterioles.[80] Although the disease is seen most commonly in young adult women it has been reported in infants and young children[81, 82] and a familial incidence has been noted.[83] Symptoms in children often begin under the age of 3 years and include dyspnea, fatigue, and syncope.[84] There are rapidly progressive signs of pulmonary hypertension and right ventricular failure.

B. EXTRALUMINAL OCCLUSION AND/OR OBLITERATION

1. Alveolocapillary Block. Conditions producing impairment of diffusion or the alveolocapillary block syndrome are almost always associated with restrictive lung disease (i.e., diffuse interstitial fibrosis). There are serious disturbances in ventilation-perfusion ratios and arterial hypoxemia results, but arterial pCO_2 is usually normal or low because hyperventilation is characteristic of these patients, which is an effective compensatory mechanism for increasing the elimination of CO_2, although it cannot fully compensate for arterial hypoxemia.[86] Also, since CO_2 *is 20 times as diffusible as oxygen*, hypercapnia is not seen from impairment of diffusion alone.

The pneumoconioses and sarcoidosis are common examples of alveolocapillary block in adults, but a review of sarcoidosis in children showed that pulmonary symptoms are seldom severe and that there is a marked tendency to change and regression.[87] Collagen diseases, however, have been receiving more attention in children and serious pulmonary manifestations are being recognized. There have been many well-documented cases of cor pulmonale in children with rheumatoid arthritis.[88, 89] The fibrotic process in the lungs causes anatomic interference with passage of oxygen across the alveolar membrane as well as a reduction in the pulmonary vascular bed.[87] Degenerative and occlusive changes are also found in the smaller pulmonary arteries. Similar pulmonary dysfunction is seen in disseminated lupus erythematosus,[90,91] scleroderma,[100] and dermatomyositis[101,102] in children as well as in adults.

Another rare condition producing the physiologic pattern of alveolocapillary block is pulmonary alveolar proteinosis. This condition, first described in 1958, has been recognized in patients ranging in age from 2½ to 57 years. It is characterized by the intra-alveolar deposition of a proteinaceous lipid-rich material which is strongly positive with Schiff (PAS) stain. The etiology is unknown. The onset is usually insidious and the course is slowly progressive with death from cor pulmonale.

Summary and conclusions

Cor pulmonale as defined denotes an increased work load on the right heart resulting from an increased pulmonary vascular resistance which may be caused by disturbances in the structure and/or function of the airways, parenchyma of the lungs, pulmonary vessels, or thoracic cage. It does not include congenital or acquired heart disease, which may also produce alterations of the pulmonary circulation and impaired respiratory function.

Basic mechanisms involved in the pathogenesis of cor pulmonale are discussed. *The common feature in all cases of cor pulmonale is an over-all reduction of the cross-sectional area of the pulmonary vascular bed which results in an increased pulmonary vascular resistance and pulmonary arterial hypertension.* This, in turn, increases the work load on the right ventricle, causing its eventual hypertrophy and failure. The two main mechanisms responsible for reduction of the pulmonary capillary bed are: (1) alveolar hypoventilation producing hypoxemia and hypercapnia (acidemia) and (2) anatomic curtailment of the pulmonary vascular bed from occlusive and/or obliterative pulmonary vascular disease. In most cases the pulmonary vascular changes appear to be initiated primarily by vasoconstriction from functional factors (hypoxemia and acidemia) and irreversible structural changes occur secondarily. Hypoxemia and acidemia per se may perpetuate and aggravate pulmonary hypertension but do not cause irreversible changes in the pulmonary vascular bed.

An etiological classification of the causes of cor pulmonale in children has been proposed based on which major pathophysiologic derangement predominates. An un-

derstanding of the pathophysiology of the underlying pulmonary disorder initiating cor pulmonale is important for planning optimal therapy The ultimate prognosis depends on the nature and extent of the primary etiological condition but many conditions producing cor pulmonale in children may be reversed or retarded by early recognition and proper management.

REFERENCES

1 Committee of the World Health Organization Chronic cor pulmonale Report of an expert committee, Circulation 27:594 1963
2 Muller C Cardiopulmonary hemodynamics in health and disease, Springfield, 1965, Charles C Thomas, pp 104-126.
3 Muschenheim, C The growing importance of pulmonary heart disease as cause of congestive cardiac failure, Am. Rev Resp Dis 83:475 1961
4. Mitchell, R. A., Loeschcke, H H Massion, W H and Severinghaus, J W Respiratory responses mediated through superficial chemosensitive areas on the medulla, J Appl Physiol 18:523 1963
5 Mitchell, R A Loeschcke, H H Severinghaus, J W Richardson, B W and Massion, W H Regions of respiratory chemosensitivity on the surface of the medulla, Ann New York Acad Sc 109:661 1963.
6 Simmons D H Linde L M and Shapiro, B J Effect of blood gases and acid-base disturbances on the pulmonary circulation Dis Chest 48:347 1965.
7 Motley H L The mechanisms of chronic pulmonary heart disease (cor pulmonale) with and without arterial hypoxemia, Prog Cardiova Dis 1:326, 1959
8 Rudolph, A M., and Yuan, S Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes, J Clin Invest. 45:399 1966.
9 Lloyd, T C J Influence of blood pH on hypoxic pulmonary vasoconstriction, J Appl. Physiol. 21:358, 1966
10 Enson, Y Giuntini, C Lewis, M L Morris T Q Ferrer M I and Harvey R. M The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation, J Clin Invest 43 1146 1964
11 Vogel, J H. K and Blount, S. G J The role of hydrogen ion concentration in the regulation of pulmonary arterial pressure, Circulation 32 788, 1965
12 Ferrer M I and Harvey R. M Cor pulmonale GP 24:92, 1961
13 Finley J J Swenson, F W and Comroe J H J The cause of arterial hypoxemia at rest in patients with alveolar-capillary block syndrome J Clin. Invest. 41:618, 1962
14 Staub C Alveolar-arterial oxygen tension gradient due to diffusion, J Appl. Physiol 18:673 1963.
15 Evans T O Van Der Reis, L and Selzer A. Circulatory effect of chronic pulmonary emphysema, Am. Heart J 66 741 1963
16. Woolf, C. R., Gunton, R W and P l, W Cardiac output and blood volume chronic cor pulmonale Canad M A J 85 1371 1961
17 Dalfano, M J and Segal, M S Pulmonary heart disease Clinical-physiologic variants, Dis. Chest 49 15 1966.
18 Shaw D B Grover R F Reeves, J T and Blount, S. G., J Pulmonary circulation in chronic bronchitis and emphysema, Brit. Heart J 27:674 1965.
19 Ehrner L., Garland, T and Linderholm H Chronic cor pulmonale following thromboembolism. A clinical and pathological study of 3 cases, Acta Med Scandina 164:279 1959
20. Dawm S., Harlan, F and Kasperky M The blood-gas exchange and the pH in chronic pulmonary heart disease Acta Med Scandinav 172:211 1962.
21 James, W R. L. The right ventricle and pulmonary vascular obstruction in bronchitis with emphysema, Brit. Heart J 28:312 1966.
22 Royce S W Cor pulmonale in infancy and early childhood. Report on 34 patients, with special reference to the occurrence of pulmonary heart disease in cystic fibrosis of the pancreas, Pediatrics 8:255 1951
23 Goddard, R F Bronchopulmonary diseases in infants and children. The physiologic pathologic and clinical relationships, Gordon B. L., editor Clinical cardiopulmonary physiology ed. 2, New York, 1960 Grune & Stratton Inc., pp 724-743
24 Goldring, R M Fishman, A P Turino, G M Cohen H. I Denning, C R and Anderson, D H Pulmonary hypertension and cor pulmonale in cystic fibrosis of the pancreas, J Pediat 65:501 1964
25. Bowden, D H Fischer V W and W tt J P Cor pulmonale in cystic fibrosis A morphometric analysis Am J Med 38:226, 1965
26. Moss, A J Harper W H Dooley R K Murray J F and Mack, J R Cor pulmonale in cystic fibrosis of the pancreas. J Pediat 67 797 1965
27 Andrews, A H. Bronchial obstruction bronchitis, and bronchiolitis, Gordon,* pp 704-7 3
28 Reynolds, E O R Arterial blood g tensions in acute disease of the lower respiratory tract in infancy Bri M J 1 1192 1963
29 Richards, W and P rck, J R Death from asthma in children Am J Dis Child 110:4 1965.
30 Griffin, J T Kass I and Hoffman M S Cor pulmonale associated with symptoms and signs of asthma in children, Pediatrics 24:54 1959
31 Bates, D V and Christie R V Respiratory function in disease Philadelphia 1964 W B Saunders Company pp 170-236
3 Menashe, V D Farrehi, C and Miller M H poventilation and pulmonale due

chronic upper airway obstruction, J. Pediat. 67 198, 1965.
33. Cox, M. A., Schiebler, G. L., Taylor, W. J., Wheat, M. W., Jr., and Krovetz, L. J.: Reversible pulmonary hypertension in a child with respiratory obstruction and cor pulmonale, J. Pediat. 67: 192, 1965.
34. Luke, M. J., Mehrizi, A., Folger, G. M., and Rowe, R. D.: Chronic nasopharyngeal obstruction as a cause of cardiomegaly, cor pulmonale and pulmonary edema, Pediatrics 37: 762, 1965.
35. Morgan, A. D.: Personal observation.
36. Logan, W. D., Jr., Abbott, O. A., and Hatcher, C. R., Jr.: Kartagener's triad, Dis. Chest. 48:613, 1965.
37. Avery, M. E., Riley, M. C., and Weiss, A.: The course of bronchiectasis in childhood, Bull. Johns Hopkins Hosp. 109:20, 1961.
38. Van den Brande, J. L.: Idiopathic diffuse interstitial pulmonary fibrosis (Hamman-Rich syndrome) in childhood, Maandschr Kindergeneesk. 30:95, 1962.
39. Weingartner, L.: Diffuse interstitielle progressive Lungenfibrose im Kindesalter. Beobachtungen an zehn Fällen, Deutsche med. Wchnschr. 90:511, 1965.
40. Yardington, C. T., Jr.: Unilateral primary interstitial pulmonary fibrosis of unknown etiology, Arch. Int. Med. 111:612, 1963.
41. Swyer, P. R., Delivoria-Papadopoulos, M., Levison, H., Reilly, B. J., and Balis, J. U.: Pulmonary syndrome of Wilson and Mikity, Pediatrics 36:374, 1965.
42. Harvey, R. M., and Ferrer, M. C.: A clinical consideration of *cor pulmonale*. *Symposium* on congestive heart failure, American Heart Association Monograph No. 1, p. 77, New York, 1960, American Heart Association.
43. Casey, J. F.: Chronic cor pulmonale associated with lipoid pneumonia, J.A.M.A. 177: 896, 1961.
44. Bates, D. V., and Christie, R. V.: Respiratory function in disease, Philadelphia, 1964, W. B. Saunders Company, pp. 374-408.
45. Levinsky, L.: Tuberculosis and cardiopulmonary failure, Dis. Chest 40:564, 1962.
46. Schuler, D.: Essential pulmonary hemosiderosis, Ann. Paediat. 192: 107, 1959.
47. Soergel, K. H.: Idiopathic pulmonary hemosiderosis. Review and report of two cases, Pediatrics 19: 1101, 1957.
48. Andrews, C. E.: Systemic diseases with pulmonary manifestations, *in* Baum, G. L., editor: Textbook of pulmonary diseases, Boston, 1965, Little Brown & Company, pp. 616-626.
49. Lukas, D. S., and Plum, F.: Pulmonary function in patients convalescing from acute poliomyelitis with respiratory paralysis, Am. J. Med. 12:388, 1952.
50. Sarnoff, S. F., Whittenberger, J. L., and Affeldt, J. E.: Hypoventilation syndrome in bulbar poliomyelitis, J.A.M.A. 147:30, 1951.
51. Gilroy, J., Cahalan, J. L., Berman, R., and Newman, M.: Cardiac and pulmonary complications in Duchenne progressive muscular dystrophy, Circulation 27:484, 1963.
52. Kilburn, K. H., Eagan, J. T., Sieker, H. D., and Heyman, A.: Cardiopulmonary insufficiency in myotonic and progressive muscular dystrophy, New England J. Med. 261: 1089, 1959.
53. Feltman, J. A., Newman, W., Schwartz, A., Stone, D. J., and Lovelock, F. J.: Cardiac failure secondary to ineffective bellows action of the chest cage, J. Clin. Invest. 31: 762, 1952.
54. Robin, E. D., and Bromberg, P. A.: Pulmonary insufficiency, *in* Safar, P., editor: Clinical anesthesia. Respiratory therapy, Vol. 1, Philadelphia, 1965, F. A. Davis Company, pp. 1-12.
55. Fischer, J. W., and Dolehide, R. A.: Fatal cardiac failure in persons with thoracic deformities, Arch. Int. Med. 93:687, 1954.
56. Snider, G. L., Miller, G., Miller, B., and Ellisberg, F. I.: Kyphoscoliotic cardiopulmonary disease. A reappraisal, (Abstract) Am. Rev. Tuberc. 78:325, 1958.
57. Carr, J. G.: The cardiac complications of Trichterbrust, Ann. Int. Med. 6:685, 1933.
58. Chapman, E. M., Dill, D. B., and Graybiel, A.: The decrease in functional capacity of the lungs and heart resulting from deformities of the chest. Pulmonocardiac failure, Medicine 18: 167, 1939.
59. Polgar, G., and Koop, C. E.: Pulmonary function in pectus excavatum, Pediatrics 32:209, 1963.
60. Hinshaw, H. C., and Garland, L. H.: Diseases of the chest, ed. 2, Philadelphia, 1963, W. B. Saunders Company, pp. 447-465.
61. Bruce, T.: Cor pulmonale as a sequel of thoracoplasty, Acta Tuberc. Scandinav. 19: 142, 1945.
62. Morgan, A. D., Bartley, T. D., and Swenson, E. D.: Respiratory impairment following thoracoplasty. Case report in a child, with comment on prognosis, Dis. Chest. In press.
63. Rowley, P. T., Mueller, P. S., Watkin, D. M., and Rosenberg, L. E.: Familial growth retardation, renal amino-aciduria and cor pulmonale. I. Description of a new syndrome with case reports, Am. J. Med. 31: 187, 1961.
64. Finkelstein, J. W., and Avery, M. E.: The Pickwickian syndrome. Studies on ventilation and carbohydrate metabolism: Case report of a child who recovered, Am. J. Dis. Child. 106:251, 1963.
65. Auchincloss, J. H., Jr., and Gilbert, R.: The cardiorespiratory syndrome related to obesity: Clinical manifestations and pathologic physiology, Prog. Cardiovas. Dis. 1: 423, 1959.
66. Cayler, G. G., Mays, J., and Riley, H. D., Jr.: Cardiorespiratory syndrome of obesity (Pickwickian syndrome) in children, Pediatrics 27:237, 1961.
67. Morris, J. J., Black, F. O., and Stephenson, E. E., Jr.: The fate of the unexpanded lung in congenital diaphragmatic hernia, Dis. Chest 48:649, 1965.
68. Oyamada, A., Gasul, B. M., and Holinger, P. H.: Agenesis of the lung. Report of a case

ith review of all previously reported cases, Am. J. Dis. Child. 85:182, 1953
69. Fishman, A. P., Turino, G. M., and Bergofsky, E. H.: Syndrome of alveolar hypoventilation, Am. J. Med. 23:333, 1957.
70. Rodman, T., and Close, H. P.: The primary hypoventilation syndrome, Am. J. Med. 26:808, 1959.
71. Rodman, T., Resnick, M. E., Berkowitz, R. D., Fennelly, J. F., and Olivia, J.: Alveolar hypoventilation due to involvement of the respiratory center by obscure disease of the central nervous system, Am. J. Med. 32:208, 1962.
72. Fishman, L. S., Samson, J. H., and Sperling, D. R.: Primary alveolar hypoventilation syndrome (Ondine curse), Am. J. Dis. Child. 110:155, 1965.
73. Arias-Stella, J., and Recavarren, S.: Right ventricular hypertrophy in native children living at high altitude, Am. J. Path. 41:55, 1962.
74. Sime, F., Banchero, N., Peñaloza, D., Gamboa, R., Cruz, J., and Marticorena, E.: Pulmonary hypertension in children born and living at high altitudes, Am. J. Cardiol. 11:143, 1963.
75. Hultgren, H. N., Kelly, J., and Miller, H.: The pulmonary circulation in acclimatized man at high altitude, J. Appl. Physiol. 20:233, 1965.
76. Hultgren, H. N., Kelly, J., and Miller, H.: Effect of oxygen upon pulmonary circulation in acclimatized man at high altitude, J. Appl. Physiol. 20:239, 1965.
77. Vogel, J. H. K., Weaver, W. F., Rose, R. L., Blount, S. G., Jr., and Grover, R. F.: Pulmonary hypertension on exertion in normal man living at 10,150 feet (Leadville, Colorado), Med. Thorac. 19:461, 1962.
78. Newman, R. W., Taranilla, G., and Chai, H. C.: Congenital absence or hypoplasia of pulmonary artery, J. Thoracic & Cardiovas. Surg. 47:740, 1964.
79. Gray, J. N. C., and Timmes, J. J.: Congenital diseases caused by anomalous pulmonary vasculature, pleural fissures, and thoracic cage, in Baum,[9] pp. 638-645.
80. Pool, P. E., Vogel, J. H. K., and Blount, S. G., Jr.: Congenital unilateral absence of pulmonary artery, Am. J. Cardiol. 10:706, 1962.
81. Arias-Stella, J., and Saldaña, M.: The muscular pulmonary arteries in people native to high altitudes, Fifth Annual Conference on Research of Emphysema, Aspen, 1962, Med. Thorac. 19:484, 1962.
82. Yater, W. M., and Hansmann, G. H.: Sickle cell anemia: A new cause of cor pulmonale. Report of two cases with numerous disseminated occlusions of the small pulmonary arteries, Am. J. M. Sc. 191:474, 1936.
83. Streeper, R. B.: Thromboembolic complications of rheumatic fever in childhood, Dis. Chest. 46:61, 1964.
84. Gasul, B. M., Arcilla, R. A., and Lev, M.: Heart disease in children. Diagnosis and treatment, Philadelphia, 1966, J. B. Lippincott Company, pp. 1309-1321.
85. Rodriquez, H. F., Fernandez Durán, A., García-Molmer, L., and Rivera, E.: Cardiopulmonary schistosomiasis, Am. Heart J. 65:253, 1963.
86. García-P. Imíeri, M. R.: Cor pulmonale due to Schistosoma mansoni, Am. Heart J. 68:714, 1964.
87. Sperling, D. R., Patrick, J. R., Anderson, F. M., and Fyler, D. C.: Cor pulmonale secondary to ventriculoauriculostomy, Am. J. Dis. Child. 107:308, 1964.
88. Friedman, S., Zita-Gozum, C., and Chatten, J.: Pulmonary vascular changes complicating ventriculovascular shunting for hydrocephalus, J. Pediat. 64:305, 1964.
89. Durham, J. R., Ashley, P. F., and Dorencamp, D.: Cor pulmonale due to tumor emboli. Review of literature and report of a case, J.A.M.A. 175:757, 1961.
90. Gasul et al.,[84] pp. 941-953.
91. Fadell, E. J., and Edwards, W. M.: Idiopathic pulmonary hypertension. Report of a case, Pediatrics Digest, July, 1963, pp. 45-50.
92. Wilson, R. A.: Idiopathic pulmonary hypertension in infants and children, Pediat. Clin. North America, May, 1958, pp. 337-353.
93. Husson, G. S., and Wyatt, T. C.: Primary pulmonary obliterative vascular disease in infants and young children, Pediatrics 23:493, 1959.
94. Thilenius, O. G., Nadas, A. S., and Jockin, H.: Primary pulmonary vascular obstruction in children, Pediatrics 36:75, 1965.
95. Melmon, K. L., and Braunwald, E.: Familial pulmonary hypertension, New England J. Med. 269:770, 1963.
96. Comroe, J. H., Forster, R. E., DuBois, A. B., Briscoe, W. A., and Carlsen, E.: The lung: clinical physiology and pulmonary function tests, ed. 2, Chicago, 1963, Year Book Medical Publishers, pp. 49-50.
97. McGovern, J. P., and Merritt, D. H.: Sarcoidosis in children, in Levine, S. Z., editor: Advances in pediatrics, Vol. VIII, Chicago, 1956, Year Book Publishers, Inc., pp. 97-135.
98. Brinkman, G. L., and Chaikof, L.: Rheumatoid lung disease. Report of a case which developed in childhood, Am. Rev. Resp. Dis. 80:732, 1959.
99. Jordan, J. D., and Snyder, C. H.: Rheumatoid disease of the lung and cor pulmonale. Observations in a child, Am. J. Dis. Child. 108:174, 1964.
100. Jordan, J. D.: Cardiopulmonary manifestations of rheumatoid disease in childhood, South. M. J. 57:173, 1964.
101. Onodera, S., and Hill, J. R.: Pulmonary hypertension. Report of a case in association with rheumatoid arthritis, Ohio M. J. 61:141, 1965.
102. Benedek, T. G., and Rodnan, G. P.: Pulmonary involvement in systemic rheumatic diseases, in Harris, M. C., and Shure, N., editors: Sensitivity and chest diseases, Philadelphia

delphia, 1964 F A. D vis Company pp. 234-254

103. Alarcon Segovia, D and Alarcon, D G. Pleuro-pulmonary manifestations of systemic lupus erythematosus, Dis. Chest. 39 7 1961

104. Huang, C. T Hen igar G R. and Lyons, H A. Pulmonary dysf nction in systemic lupus erythematosus, New England J Med. 272:288, 1965.

105 Kass, H., Hanson V nd Patrick, J Scleroderma in childhood, J Pediat 68:243 1966.

106. Cald ell, I W and Aitchison J D Pulmonary hypertension in dermatomyositis, Brit. Heart J 18:273, 1956

107 Wedgwood, R. J P Cook, C. D and Cohen, J : Dermatomyositis. Report of 26 cases in children, with discussion of endocrine ther py in 13 Pediatrics 12:447 1953.

108. Coates, E. O J Pulmonary diseases of suspected allergic etiology I Harris and Shure, pp 255-278.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reappraisal of digitalis Part VIII Digitalis dosage

Alan F. Lyon, M.D.
*Arthur C. DeGraff, M.D.***
New York, N. Y.

Because of the complexity and variability of the metabolism of the cardiac glycosides, the individual characteristics of glycosides themselves, the marked variation in their action from patient to patient, and the difficulty in assessing their inotropic effect in man, the adjustment of digitalis dosage must necessarily be individualized and largely empirical. The problem is further complicated by the fact that the therapeutic dose of digitalis and the glycosides is between 35 and 65 per cent of the toxic dose. Such a narrow therapeutic range is not to be found with most other potent substances used today in medicine. The therapeutic range is further reduced when digitalis is used in conjunction with diuretics which cause the depletion of potassium. Nonetheless, extensive clinical use has produced information concerning the average dose range of dosage and onset and dissipation of clinical effect that can serve as guidelines to the physician.

The rapid-acting glycosides. When a prompt digitalis effect is required, as in the treatment of certain arrhythmias and in severe pulmonary edema, a rapid-acting glycoside should be administered intravenously. Ouabain and deslanoside are the glycosides of choice. Although deslanoside is commonly used in this country and is, indeed, measurably effective in less than 15 minutes, ouabain is preferred because of its greater speed of action. Deslanoside does not produce the maximal effect of a single dose for about 4 hours. After an initial dose of 0.8 mg., it is unwise to administer further increments for 2 hours, and 4 hour intervals are safer still. Since the therapeutic dose may range from 0.8 to 2.0 mg., effective levels may not be achieved for as long as 16 hours. Ouabain, on the other hand, has a measurable effect within 5 minutes and achieves maximal clinical effect, as estimated by control of ventricular rate in atrial fibrillation, in about 1½ hours. Moreover, recent studies suggest that the peak of ventricular irritability after toxic doses occurs between 25 and 35 minutes after the last dose and decreases thereafter. It is possible, therefore, to administer additional intravenous doses at half hour intervals. Full effect can thus be achieved rapidly and safely in a few hours. The range of therapeutic dose is 0.5 to 1.2 mg. An initial dose of 0.5 mg. may, as a rule, be given safely in the undigitalized patient, and 0.1 mg. may be given thereafter every half hour until the desired effect is achieved or toxicity occurs. In the aged and in

Received for publication Jan. [illegible] 1967.

*Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N. Y.
**Professor of Therapeutics, New York University School of Medicine, and Consultant in Cardiology, Veterans Administration Hospital, Bronx, N. Y.

patients with electrolyte derangements serious toxicity can occur after the first dose therefore in these patients the initial dose should not exceed 0.3 mg. When digitalis effect is needed rapidly but not urgently 1.0 mg. of digoxin can be given intravenously. The clinical onset of action of this agent employed intravenously is nearly as rapid as that of deslanoside the advantage of its use is that digitalization can be continued at 6-hour intervals with oral digoxin. The difficulties encountered in transition from deslanoside or ouabain to oral glycoside are thus avoided.

Long-term digitalis therapy—the loading dose. Although differences of opinion exist as to the rapid intravenous use of cardiac glycosides they are minor compared to the varieties of opinion about the long-term use of digitalis. Since the time of Eggleston 50 years ago most clinicians have agreed on the need for a loading or digitalizing dose at the onset of glycoside therapy. Studies with C 14 digitoxin and digitoxin bioassay 10 to 15 years ago suggested that there was an absolute limit to the amount of digitalis that could be excreted daily and thus supported the hypothesis involved in a loading dose. On the other hand one author has reported on a large series of patients with atrial fibrillation who were digitalized rapidly with intravenous preparations. Some were then redigitalized with loading doses of oral glycosides and put on a maintenance dose others were placed directly on a maintenance dose. After a week, the ventricular rates were comparable in the two groups. Furthermore a recent laboratory study was reported to show that the blood level of tritiated digoxin was the same 7 days after the onset of treatment whether there was or was not a loading dose.

Nonetheless it would appear that a loading or digitalizing dose is desirable with all oral glycosides. We have observed that in patients tolerant to digoxin, toxic symptoms have occurred 1 or 2 weeks after digoxin 0.5 mg four times a day was begun. This is clear evidence of accumulation. Also it has been noted in the case of atrial fibrillation that, when the heart rate is slowed by rapidly dissipated intravenous glycosides, additional oral glycoside beyond the ultimate maintenance dose is necessary to control the ventricular rate. Finally even if there were no accumulation of glycosides, the hemodynamic effects of initial full digitalization are so striking that it would be warranted in any case to speed the improvement of the patient.

Technique of the initial digitalization. It is our practice to use digoxin as the routine oral glycoside. We limit the use of other glycosides to special situations. The duration of the effect of digoxin is persistent enough to permit single daily administration even in patients with atrial fibrillation and brief enough that, should toxicity occur the duration will not be greater than a day or two. This represents a distinct advantage over the use of either digitoxin or digitalis leaf.

Although it has been said that digoxin by mouth is only half as effective as digoxin by the parenteral route it has been our experience that the dosage in the two modes of administration is quite similar. This is supported by recent metabolic studies with tritiated digoxin.

The range of the loading dose of digoxin varies considerably from patient to patient. However clinical studies have demonstrated that the average digitalizing dose when digoxin is administered initially at the rate of about 1.5 to 2.0 mg a day is about 3.0 mg. In patients who are electively digitalized it is reasonable to administer such a dose in a fractional manner beginning with no more than 1.5 mg followed by 0.5 mg every 6 hours and if the desired clinical effect is achieved the average maintenance dose of 0.5 mg daily in most adult patients, or 0.25 mg daily in aged or uremic patients, is begun. Clinical observation will determine further adjustments of the maintenance dose.

In the more severely ill patients who are hospitalized and in whom maximum digitalis effect is desired it is our practice to administer an initial dose of 1.0 mg and then 0.5 mg every 6 hours. Moreover since such patients are also being treated with bedrest, salt restriction and diuretics it is often impossible to define the therapeutic effect that is due to digitalis. The loading schedule of digitalis must, therefore continue until minor toxicity occurs. In a series of 200 patients so digitalized

with digoxin reported by one of us the procedure proved to be safe (85 per cent manifested only gastrointestinal toxicity) and a wide range of digitalis requirement was demonstrated Whereas the median toxic dose was 4.5 mg the mean was 6.0 mg the toxic dose varied from 1.0 to 6.4 mg

It is essential during such digitalization that the patient be assessed for minor toxicity before each dose by an experienced nurse or by the physician and that even when no other toxicity is apparent, an electrocardiogram should be recorded daily

The maintenance dose There is a close correlation between the loading dose and the maintenance dose. Patients who tolerate an average dose of digoxin as a loading dose can be safely started on a maintenance therapy of 0.5 mg a day those whose initial dose is less than the average 0.25 mg a day and those who require more than the average, 0.75 or 1.0 mg a day Further observation is necessary to establish the actual maintenance dose. A dose as low as 0.125 mg a day may be desirable for an occasional aged or uremic patient, whereas other patients may require and tolerate as much as 1.25 mg a day

Other glycosides Clinical experimentation has demonstrated average therapeutic digitalizing doses of 2.5 Gm for digitalis leaf and of 2. mg for digitoxin. A wide range of actual requirements similar to that for digoxin exists but the long duration of toxic effects makes digitalization to toxicity more hazardous. The average maintenance dose is 0.15 mg for digitoxin and 0.15 Gm. for digitalis leaf The range is 0.05 to 0.3 Gm. for leaf and 0.03 to 0.3 mg for digitoxin We have observed several patients who require and tolerate as much as 0.4 Gm of digitalis leaf Gitalin has value in patients who suffer prominent and early gastrointestinal toxicity from digoxin. In such patients, more effective digitalis therapy can sometimes be accomplished with this mixture of water-soluble glycosides.

Summary In long term digitalis therapy it is important to assess the dose regularly and to adjust it on the basis of clinical observation. Increasing symptoms and signs of heart failure are always indications for a trial of an increased dose of the cardiac glycoside rather than for the immediate institution of diuretic therapy

REFERENCES

1 Marcus, F I Burkhalter L. Cuccia, C P ovich J and Kapadia, G C Administration of tritiated digoxin with and without loading dose A metabolic study Circulation 34:865 1966.
2 Rosenblum H Maintenance of digitalis effects after rapid parenteral digitalization J A M A. 182 192 1962
3 Kay C F The clinical use of digitalis preparations, Circulation 12:291 1955
4 DeGraff A C Indications for and use of the cardiac glycosides, Postgrad Med 18:40 1955

Annotations

Changes in the natural history of hypertensive disease

In 1955 a prospective study of hypertensive disease was begun at the Cardio-Vascular Clinic, Sydney Hospital, N.S.W., Australia. Since then, over 1,000 patients have been investigated and the majority kept under regular review. Over 95 per cent of all subjects with severe hypertension (diastolic blood pressure of 110 mm. Hg or more) have been followed to the end of their disease or are still attending the Clinic. In the course of this study the impression was gained that certain changes were taking place in the type of patient referred to the Clinic and in the diagnosis, prognosis, and management of hypertensive disease. Therefore, a comparison was undertaken between the first 100 patients seen in 1955 and 100 patients seen after January 1, 1960.

Patients were referred from other hospital departments, private and consulting practices of physicians attending the Clinic, and from outside doctors. They were initially interviewed by the Clinic sister and secretary who recorded the vital data, obtained details of past history and family history, and arranged appointments for laboratory tests. Routine investigations included electrocardiography, x-ray examination of the chest, renal function tests, estimation of renal size and, in recent years, isotope renography. The patients were then seen by a physician who carefully checked the history and carried out a full physical examination. Blood pressures were taken in both arms by a member of the nursing staff and the physician with the patient in the recumbent and standing postures. The diastolic readings were measured to the disappearance of the Korotkoff sounds. Ocular fundi were examined after full dilatation of the pupils with mydriatics, unless specifically contraindicated, and also independently assessed by a member of the ophthalmic staff. For some time, retinal photography was carried out as a routine procedure. Special tests, including detailed assessment of renal function, intravenous pyelography, renal arteriography, and estimations of catecholamines, were ordered as indicated. Each patient, when fully investigated, was discussed at the weekly clinic conference and recommendations with regard to therapy were then considered. Arrangements were made for regular follow-up examinations, and each patient was re-evaluated in detail at least once a year.

In order to study changes in the natural history of hypertensive disease, 100 consecutive patients of the 1955 and 1960 groups were compared. The only selection exercised was the exclusion of patients who were over the age of 60 at the time of their first attendance at the Clinic. Details of the patient material have been given elsewhere.

Careful enquiry into the results of life insurance, superannuation, and army medical examinations, history of pregnancies, and inspection of hospital records revealed frequently the existence of hypertension many years prior to referral of the patients to our Clinic. Thirty patients in our 1955 group had already been hypertensive for at least 10 years before coming to the Clinic. Of these, 18 are still alive, many free of symptoms after 20 years of hypertension. The mortality rate in this group is comparable to that of the entire series, which indicates that the duration of hypertension is of little prognostic significance in the individual patient.

The importance of the ocular fundi in the prognosis of hypertension has been recognized for many years. The 1955 group included 17 patients with papilledema, and an additional 16 patients with hemorrhages and exudates. The figures for the 1960 group were 9 and 13 patients respectively. Fewer patients with accelerated hypertension are now being referred to the Clinic. It is a matter of speculation whether this fall-off represents a true reduction in the incidence of the malignant form of hypertension in recent years.

Electrocardiography was the most useful single test of hypertensive cardiac involvement. In the year-to-year analysis it was a more reproducible index of cardiac enlargement than either physical examination or chest radiography. It is of interest that the 1955 group contained more patients with the severer grades of left ventricular hypertrophy than did the 1960 group.

In recent years a larger percentage of patients referred to the Clinic had evidence of renal failure. Twenty-four per cent of the 1960 group had persistent elevation of blood urea nitrogen, as compared to 18 per cent in the 1955 group. This may partly be explained by the development of a special interest in renal disease within Sydney Hospital.

The presence of established cardiac and cerebral complications at the time of referral to the Clinic obviously influences the ultimate survival statistics. The incidence of cardiac complication was similar in the two groups. Cerebrovascular complications

however were more common in the 1955 group and may partly explain changes in the mortality patterns in the two groups.

A study of the family history was of interest. When this project began it was not appreciated that positive family history was no more common in primary hypertension than in some forms of so-called renal hypertension. Irrespective of the ultimate validity of the criteria for the diagnosis of glomerulonephritis, chronic pyelonephritis, and toxemia of pregnancy adopted in this study it is obvious that a family history of hypertension or premature vascular disease is no argument in favor of primary hypertension. A possible interpretation of this finding may be that hypertension is genetically predetermined disorder and that, in the majority of instances, pyelonephritis and toxemia are etiologically unrelated or at best are precipitating or aggravating factors.

There have been striking changes in the prognosis of the 1955 and 1960 groups. Three-year mortality rates have shown reduction from 31 to 14 per cent. Young, reviewing some of the Clinic earlier material, found that the four factors which most clearly affected prognosis in an adverse fashion were high degree of retinopathy the presence of renal failure, very much elevated blood pressure and the presence of cardiac and cerebral complications.

In the course of the study it became apparent that the symptom headache was of no prognostic significance. Over 60 per cent of all patients attending the Clinic complained of this symptom. Follow-up studies showed that the mortality rate among those free from headache was slightly greater than among those complaining of this symptom.

Analysis of the causes of death showed an interesting trend. In the 1955 group over half the patients died from strokes, whereas in the 1960 group, only 1 of the 13 deaths was due to cerebral thrombosis or hemorrhage. This high incidence in the 1955 series is partly attributable to the large number of patients with established cerebrovascular disease included in the first series. Yet even when allowance is made for this factor there appears to be little doubt that the number of fatal cerebrovascular accidents has been significantly reduced as result of more consistent lowering of the blood pressure. Nowadays, nearly half the patients succumb to cardiac complications, especially myocardial infarction.

It is an impression, as yet not statistically confirmed, that adequate treatment has modified the natural course of the disease. There appears to have been substantial reduction in blood pressure figures improvement in the ocular fundal gradings some decrease in cardiac size with diminution of electrocardiographic signs of left ventricular hypertrophy and delay in the appearance of major vascular complications, especially with regard to the cerebral circulation. The outlook for patients with accelerated hypertension, in the absence of advanced renal failure, has shown striking improvement. One disturbing feature was the gradual rise in the level of blood urea nitrogen observed at annual review tests, which is indicative of slowly progressive deterioration of renal function. This appeared to be often independent of the success of control of the blood pressure.

In summary, the most significant changes that have been observed in this large population of hypertensive patients during the past decade were fall in the incidence of accelerated hypertension, with significantly increased length of survival, marked drop in mortality due to cerebrovascular accidents, and an apparent improvement in the over-all prognosis. With the introduction of modern investigational methods there has been widening of the diagnostic range, and with the availability of new drugs an increased choice and sophistication of treatment.

G. E. Bauer, M.R.C.P., F.R.A.C.P.
Cardio-Vascular Clinic
Sydney Hospital
185 Macquarie St.
Sydney, Australia

REFERENCES

1. Bauer, G. E.: The changing pattern of hypertensive disease, M. J. Australia 1:698, 1966.
2. Young, A. A.: Unpublished data, 1964.

The natural history of cerebral berry aneurysms

At present, we know about the structure of aneurysms and their known certain association with medial defects, but we know little of their natural history, mechanism of rupture, or cessation of bleeding, and even less about their pathogenesis and the relative importance of the various factors concerned.

Aneurysms from 249 patients who died from ruptured cerebral aneurysm were examined. One hundred and fifteen were unruptured, and 289 were ruptured.

It was found that the critical size beyond which aneurysms became unstable and likely to rupture was maximum external diameter of 4 mm.

The finding that the majority of ruptures occurred at the apex or dome of aneurysms confirmed Crawford's original finding. The greater proportion of posterior communicating aneurysms with ruptures through the body or neck might be explained by the broad necks and sessile shapes of these aneurysms, rendering distinct subdivision into neck, body, and apex more difficult.

It appears that the larger multiloculated aneurysm is more likely to rupture than the smaller unloculated one. The important factor here is very probably the size rather than the multiloculation. Multiloculation appears to indicate something of an aneurysm's past history but little of its future.

The majority of aneurysms had ruptured by the time they achieved a maximum external measurement of 15 mm., and any that were larger than this were ruptured in the present series. Thus there was no evidence for the impression that very large aneurysms are stable and unlikely to rupture. This has probably arisen from cases in which a large aneurysm has produced symptoms and signs of compression of cranial nerves and brain before it could rupture.

It was thought that aneurysms could arise at any time in life and increase rapidly in size. This makes the onset of vascular hypertension at any age a possible factor in the initiation as well as the enlargement of cerebral aneurysms and supports the case of an aneurysm arising de novo in an adult reported by Graf and Hamby. However, undoubtedly some aneurysms do commence early in life (the third decade) and do not rupture until late (the eighth decade).

The finding that, in 88 per cent of cases of subarachnoid hemorrhage with multiple cerebral aneurysms, the largest aneurysm had ruptured is of value in the interpretation of angiographs, and the direction of surgery.

It was found that there was a tendency in ipsilateral combinations of middle cerebral and internal carotid aneurysms for the proximal aneurysm to have ruptured. This supported the hypothesis put forward by Jain that the presence of a proximal aneurysm damped the distal pulsation and rendered a distal aneurysm less likely to rupture. This did not apply to combinations of internal carotid and anterior communicating aneurysms, in which the collateral flow and pulsation from the opposite anterior cerebral stem appeared to be adequate to nullify any damping of pulsation by the internal carotid aneurysm.

Examination of a series of unruptured aneurysms suggested that a change consisting of cellular and fibrinous infiltration of the wall of the aneurysm occurred in a minority of them, and that a similar appearance was present adjacent to the rupture in all ruptured aneurysms.

It is suggested that this change results in weakening of the wall of the aneurysm. This may then give way and enlarge the aneurysm and then organize, perhaps forming a bubble or secondary loculus in which mural thrombus might organize and acquire an atheromatous appearance. Alternatively blood constituents may seep or dissect through the affected wall of the aneurysm into the cerebrospinal fluid, as was seen to occur in the present series, and as was suggested by Falconer[3] and others. This may proceed to frank rupture or it may organize and heal, with possible enlargement of the aneurysm and thickening of the adventitial component of the wall of the aneurysm, and if mural thrombus forms, thickening of the intima and perhaps atheroma-like changes within it.

These changes in the walls of aneurysms resemble the subendothelial polymorph permeation of cerebral arteries which accompanies stasis due to vasospasm and proximal occlusion due to emboli and other causes. It also resembles the basophilic intimitis of Sheehan and Moore, which they attributed to stasis in the small renal arteries, and which was confirmed experimentally in rabbits by Sheehan and Davis. Thus it appears to accompany intimal damage. This damage may be ischemic as in these arteries, or possibly mechanical, due to changes in pulsatile pressure in a relatively inelastic sac or turbulent flow in an aneurysm. In aneurysms an ischemic factor may be added when plasma gets through a breach in the endothelium and permeates the wall, or mural thrombus impairs the diffusion of oxygen and metabolites into the wall of the aneurysm. Wood produced angiographic evidence of the retention of angiographic contrast material at the periphery of aneurysms, especially large ones. This suggests turbulent flow with friction between the wall and blood such as does not occur with axial flow and which with resultant stasis and endothelial trauma might reasonably be expected to result in the formation of mural thrombus. Unless atheroma was present when vasa vasora appeared, no vessels were seen in the walls of any aneurysm. The same is true of the thin-walled cerebral arteries from which they arise. Thus, all nutrition is obtained by diffusion from the lumen.

It is considered that these changes in the walls of aneurysms represented the sequelae of damage to the walls, and that they might lead to distention, rupture, or thickening of the wall of the aneurysm with possible atheroma-like changes ensuing. The sequence of events is probably very similar to the formation of some types of atheromatous plaques elsewhere in the vascular system.

M. R. Crompton, M.D., Ph.D.
Department of Pathology
St. George's Hospital Medical School
London, S.W. 1, England

REFERENCES

1. Crawford, T.: Some observations on the pathogenesis and natural history of intracranial aneurysms, J. Neurol. Neurosurg. & Psychiat. 22:259, 1959.
2. Crompton, M. R.: The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms, Brain 87:491, 1964.
3. Falconer, M. A.: Surgical pathology of spontaneous intracranial hemorrhage due to aneurysm and arteriovenous malformations, Proc. Roy. Soc. Med. 47:693, 1954.
4. German, W. J., and Black, S. P. W.: Intra-aneurysmal hemodynamics: turbulence, Tr. Am. Neurol. A. 79:163, 1954.
5. Graf, C. J., and Hamby, W. B.: Report of a case of cerebral aneurysm in an adult develop-

ing apparently de novo, J Neurol Neurosurg & Psychiat. 27 153, 1964.
6. Jain, K. K.: Mechanism of rupture of intracranial saccular aneurysms, Surgery 54:347 1963.
7. Sheehan, H. L., and Davis, J. C. Complete permanent renal ischemia, J Path. Bact. 6:569 1958.
8. Sheehan H L., and Moore, H. C. Renal cortical necrosis and the kidney of concealed accidental haemorrhage Oxford, 1953, Blackwell Scientific Publications.
9. Wood, E. H. Angiographic identification of the ruptured lesion in patients with multiple cerebral aneurysms, J Neurosurg 21 182, 1964.

The long term therapy of severe hypertension with guanethidine

E aluation of the effectiveness of modern hypotensi drugs is confused by the tendency of many physicians to use them in combination, and to supplement their action with thiazide diuretics, which themselves have hypotensive properties.

A study was undertaken, therefore, t test the long term effectiveness of guanethidine (Ismelin Ciba) used alone in patients with severe hypertension. Selection of patients was confined to those who had diastolic blood pressures consistently over 120 mm. Hg, were 55 years of age or less, had good renal function, and were without obvious complications of therosclerosis. T enty-one females and 14 males, who had an erage age of 46 years, were studied for periods of up to 5 years.

Guanethidine was given orally generally in single dose in the morning, although a few patients preferred to divide their daily dose in order to reduce hypotensive symptoms. The blood pressure was recorded after patients had been standing for t least 5 minutes, and again after a brisk walk of 50 yards. The latter technique was employed because most patients who are taking adequate guanethidine experience an appreciable f ll in systolic and diastolic pressures after exercise—in one case in this series fall from 180/125 to 115/80 mm Hg was recorded

This phenomenon has been ascribed by Dollery nd associates[1] t interference by guanethidine with the normal pressor response to exercise. Its importance is that, if the need for an increased dose of guanethidine is assessed solely from the standing blood pressure (or worse still from the recumbent reading), dangerous hypotension can be produced after exercise. It is strongly recommended that all patients taking guanethidine be adequately exercised t each visit hen fall in blood pressure occurs fter exercise the prescribed dose of guanethidine should be determined from the lower reading

I this series, guanethidine produced an initial hypotensi response in all patients. However 17 patients (49 per cent) subsequently developed tolerance t the drug, and progressively larger doses were required to control the blood pressure. The maximum dose required was 625 mg daily but requirements of 300 mg or more ere not uncommon.

Delayed tolerance has been considered by many uthors[2-4] to occur rarely or not t all, and this may ha been due to the concurrent administration of other hypotensi agents or thiazides in their series. It was decided, therefore, to test the effect of thiazides after tolerance had emerged, and chlorothiazide was given to 5 tolerant patients whose average dose of guanethidine exceeded 250 mg.

There was no beneficial effect on the control of blood pressure, and further increases in guanethidine were necessary in 3 of the 5 cases, whereas in no patient could the dose of guanethidine be reduced. Two patients became more sensitive to guanethidine about 6 months after commencing to take chlorothiazide, the reason for which is obscure but may have been related to the onset of the hot Queensland summer Certainly it is hard t believe that chlorothiazide had anything to do with it

All the usual side effects of guanethidine were encountered, but the most distressing were exertional dizziness and muscular weakness, both of which occurred in the majority of patients, tolerant as well as nontolerant, when their blood pressure fell below 170/110 mm Hg After many months of mainte nance t satisfactory lower level of blood pressure a few patients appeared to adapt to the lower level and lost their hypotensi symptoms but in mo their persistence was more disturbing than ere the pre-treatment symptoms. This proved to be considerable problem, and despite reassurance and encouragement, several patients defa lted from the trial, probably because of the distressing symptoms.

Depression was encountered frequently female patients but responded ell to imipramine. One patient experienced loss of blood pressure control each time that imipramine as prescribed. This is thought to ha resulted from antagonism of those effects of guanethidine due to adrenergic blockade[5] and ould seem t contraindicate the use of the t drugs together

The urinary excretion of guanidine-like substances[6] was measured and found to be of no value i the control of these patients, because of the wide

and unpredictable variations in the amou ts ex creted.

Four patients died of myocardial infarction, and 4 of strokes only 2 of these were regarded as being excellently controlled and 5 of the remainder fell to the tolerant group, which suggests that good ontrol and ease of control of blood pressure may indicate better prognosis. Seventeen patients either def ulted from the trial or were withdrawn for medical reasons, e.g severe side effects, strokes, etc., and again many of these were tolerant patients with poor control of blood pressure. All 10 patients who were still attending t the conclusion of the trial had good or excellent control of blood pressure and only 2 of these suffered with signific t hypotensiv symptoms.

It seems therefore, that, despite its potency guanethidine used alone is unlikely to be satis-factory agent in the long term therapy of more than one third of you g patients with severe hypertension.

A. E. Stocks M.B. M.R.A.C.P.
Athol Robertson F.R.A.C.P.
P incess Alexandra Hospital
B isba Queensl d Australia

REFERENCES

1. Stocks, A. E., and Robertson, A.: The long term therapy of severe hypertension with guanethidine, M J Australia 1:893, 1966.
2. Dollery C. T. Emslie-Smith D. and Milne, M.D.: Haemodynamic effects of guanethidine, Lancet 2:331 1961
3. Bauer G. E., Croll, F. H. T. Goldrick, R. B. Jeremy D. Rafton, J. Whyte, H. M. and Young, A. A. Guanethidine in the treatment of hypertension, Brit. M. J. 2:410, 1961
4. Dollery C. T. Emslie-Smith, D. and Milne, M. D.: Clinical and pharmacological studies with guanethidine in the treatment of hyper tension, Lancet 2:381 1960.
5. Leishman, A. W. D. Matthews, H. L., and Smith, A. J. Antagonism of guanethidine by imipramine, Lancet 1 112, 1963

*Present address: Department of Endocrinology Royal Melbourne Hospital, Victoria, Australia.

The importance of the nerve supply to the coronary vessels in relation to myocardial ischemia and infarction

As long ago as 1924 Spalteholtz[1] described the existence in the heart of substantial network of vessels joining arious arterial branches of the coronary arterial tree. Despit this the standard teaching for many years has been that coronary arteries are end arteries, vessels leading directly i t the microcirculatory network of arterioles and capillaries with no major cross links. Blumgart and Zoll[2] state that coronary arteries must be con sidered to be end arteries in functional or physiological sense. They do not deny th existence of arterial anastomoses but mai tain that they are too small to be effective, being fine vessels of arteriolar or capillary size nd never more than 40 μ i diameter

This simple pproach would imply that total occlusion of any particular vessel would inevitably lead to cellular death in the circumscribed area supplied by it. I fact, it is common experience that the effects of occlusion are variable. Eates and associates[3] emphasize that minor occlusive disease may lead to major myocardial necrosis, whereas massive, major occlusions may occur w th minimum lesions. Moreover old occlusions which t the time produced no clinical evidence of damage may years later be associated with the production of fresh i farction They say that "these puzzling facts seem to point to nknown dynamic factors in addition t anatomic disease of the coronary vessels, as cause of the acute clinical events in this disease.

Today there is a great deal of evidenc pointing to the existence of major network of arterial anastomoses. Gömöri using microsphere perfusion methods in postmortem h man hearts, showed free comm nications larger than 100 μ i normal and in diseased hearts. F lton,[4] i an extensiv angiographic study of normal and ischemic hearts, showed extensive precapillary anastomoses and large subendocardial plexus joined to the coronary plexus through anastomotic branches. Like other workers, he found the anastomotic connections to be easier to demonstrate in the ischemic than in the healthy heart. Similar findings were reported by Eates and associates, by Rodrigues and Robles, nd by Baroldi.[?]

One must, in this context also note Gregg earlier findings[?] that, after coronary ligation retrograde flow could be demonstrated in the li-

gated vessel. There have also been a number of reports suggesting that, after acute coronary ligation, blood flow in the territory of the affected artery does not fall to zero, and that the affected area can still be perfused.[30]

It is clear that anastomoses exist which join major coronary divisions or different branches of the same division. In the normal heart they are usually thin vessels and hard to demonstrate; in the ischemic heart they are large and easy to demonstrate. Fulton[4] makes the point that, where they are found to be wide open after occlusion of a coronary artery, the ischemic damage is usually focal and relatively small; where they do not open satisfactorily the occlusion leads to massive, regional infarction. He makes the further point, of hemodynamic importance, that the ideal condition for their opening is the creation of a pressure differential between the ends of the vessel—such as would follow an acute coronary occlusion.

It would seem to be probable, however, that other factors are concerned in the patency or otherwise of coronary arterial anastomoses.

A number of attempts have been made to invoke a vasospastic factor in the development of infarction. LeRoy and Snider[31] make the categorical statement that sudden death in the case of infarction is due to reflex coronary vasoconstriction, the stimulus of which is the infarct, whose afferent pathway is the cardiosensory innervation and whose efferent pathway is the vagus.

The concept of sensory receptor sites in the coronary arteries is well substantiated by the work of Dawes.[32,33] Their role in coronary vasospasm is not so clear. Lebedinskii and associates[34] and Lapin[35] suggested that such receptors could be stimulated by local anoxia to produce reflex vasospasm in other parts of the coronary vascular bed.

On the other hand, there is a great deal of evidence purporting to refute this concept. Opdyke and Selkurt[36] could find no evidence of reduced flow in the other coronary arteries after ligating a major division. Indeed, if anything there was a net increase in flow. These findings were confirmed by West and associates,[37] and earlier by Gregg. West and associates[38] used Lycopodium spore injection methods to produce coronary occlusion and, after an extensive pharmacologic study, could find no evidence of any reflex component in the blood flow responses. Their experiments were repeated by Guzman and associates,[39] who found definite evidence of nervously mediated vasoconstriction distal to the occlusion and, moreover, came to the conclusion that West and associates' interpretation of their own data had been incorrect and that their evidence too showed vasoconstriction.

Gregg[9] makes the point that the negative experiments were performed after extensive stripping and probably denervation of the coronary arteries and in consequence, did not really provide a valid refutation of the spasm concept. A further point is that these negative experiments all measured total flow to one or the other of the coronary arteries and did not assess events in the microcirculation of the myocardium. Angiographic methods are of great value, but it was not until the introduction of heated thermocouple methods that a detailed assessment of dynamic circulatory patterns in the living myocardium became possible.[40,41] This method has aroused considerable controversy but it must now be regarded as proved and valid for the semiquantitative evaluation of the irrigation of a circumscribed area of myocardium.[42] It is not a measure of total flow but it does enable comparisons to be made between different parts of the myocardium.

Using these methods applied to the dog, Grayson and Lapin[43] re-examined the question of nervous factors in coronary infarction. They repeated Lapin's experiments using local infiltration of Novocaine into the heart and performed others using adrenergic neurone blockers and alpha blockers. The adrenergic neurone blockers used were bretylium tosylate and bethanidine sulfate, substances which prevent the release of adrenaline from sympathetic nerve endings but not from the adrenal medulla. In fact one of the difficulties in their use is that on intravenous injection they cause an immediate release of adrenaline from the adrenal medulla.[44] Consequently acute coronary ligation could not be carried out for at least 2 hours after administration of the blocking agent. The following points emerged:

1. Immediately after coronary occlusion in the untreated dog there was a 50 to 60 per cent drop in flow near the ligature. During the next 4 hours, flow slowly fell to zero.

2. After coronary occlusion in the untreated dog there was a 30 per cent hyperemia in areas more remote from the ligature. This was short lived; flow returned to initial levels, and where the recording was from the anterior ventricular wall, the flow usually fell further, in many cases reaching zero levels within 4 hours.

3. After adrenergic neurone blockade—in the deeply anesthetized animal—or infiltration of Novocaine, coronary ligation never produced infarction.

4. After adrenergic neurone blockade the hyperemia in surrounding areas was greatly increased—averaging 100 per cent—and more prolonged.

5. In lightly anesthetized animals neurone blockade was ineffective in preventing infarction.

Further work by Grayson and Parratt (unpublished) has shown that the hyperemia was not affected by beta blockade or by atropine and was probably not neurogenic.

These experiments strongly support a neurogenic factor in the final pathway of the production of infarcts. They give no support to LeRoy's suggestion that the efferent pathway is vagal, and point to increased activity of alpha receptors. In a small number of experiments Grayson and Lapin found that the alpha blocking agent [illegible] gave protection against the formation of infarcts. They attributed this to a fall in blood pressure—which by itself would militate against the opening of collaterals, coupled with increased activity of the heart muscle. However, Kovach (personal communication), gave [illegible] 24 hours before acute clamping of a coronary artery and was able to show that, under these conditions, coronary occlusion produced an initial drop in blood flow which then returned rapidly to resting levels.

There is no final evidence that receptor sites in the coronary vessels or extracardiac reflex path-

way are actually involved in infarction the massive vasoconstriction reported could equally well be due to direct stimulation of efferent nerves passing through an area of relative ischemia. It is also possible that increased sympathetic vasoconstrictor activity may be due to the inhibition of vasodilator fibers rather than to the stimulation of vasoconstrictor fibers. These are matters for further investigation.

The failure of adrenergic blocking agents to give protection in the lightly anesthetized animal was thought to be due possibly to the effects of release of adrenaline. Experiments were accordingly performed after adrenergic neurone blockade in which infusions of adrenaline were given during ligation and 2 hours afterward in the deeply anesthetized dog. It was found that adrenaline could be given 2 hours after ligation without infarction occurring; adrenaline given at the time of ligation always caused infarction.

It was thought that this probably was not directly due to action on the coronary vessels but rather to the action of adrenaline on the heart muscle—increasing its force of contraction before collaterals had time to open or other circulatory compensation to occur.

Blumgart and Zoll[2] made the point propos of angina that the pain occurred because of a temporary disproportion between the blood supply and the myocardial requirements. It might be suggested that a similar although more drastic disproportion between blood available and the metabolic requirements of the myocardium could be the trigger which initiates the final events leading to infarction.

This stimulus may be visualized as bringing about the following series of events: (1) a widespread augmentation of alpha activity, that is to say, a widespread sympathetic vasoconstriction; (2) an opposing widespread hyperemia (which could account for the various reports of increased coronary blood flow after ligation of one branch). The mechanism of this effect is unknown. It may ultimately prove to have a humoral mediation. It is powerful and in many acute occlusions, such as occur clinically, it is probably sufficient to ensure the opening of collaterals and the provision of a supply of blood to the affected muscle adequate to prevent infarction. In cases of massive occlusion in which infarction supervenes, the hyperemic process becomes slowly exhausted, first near the occlusion and then farther away. The boundaries of protective dilatation slowly shrink and leave an expanding area of cardiac muscle rendered ischemic by intensive adrenergic vasospasm.

If this approach be accepted, there are, then, three separate but equally important considerations in the infarction process, namely, the physical state of the blood vessels and the availability of blood to the myocardium, the work load of the heart, and the state of equilibrium between the divisions of the autonomic nervous system regulating the tone of the coronary vessels.

Such a scheme suggests the feasibility of a pharmacologic approach to the treatment of myocardial ischemia. Beta blocking agents, such as propranolol, have been used since 1963.[10] Propranolol, however, is a vasoconstrictor agent in the myocardium. Its beneficial action seems, nevertheless, to be established.[11] In our own laboratory administration of propranolol to experimental animals halved the infarction rate after coronary occlusion (Grayson, Parratt, and Irvine—unpublished findings). The effect of propranolol is thought to be due to the fact that it has a marked action directly on cardiac muscle—it slows the heart, reduces cardiac output, and reduces the work load.

A more direct approach is suggested by the action of adrenergic neurone blocking agents reported above. If the initial sympathicomimetic activity of such preparations could be eliminated they might well have a useful part to play in the management of cardiac ischemia. Green (personal communication) reports that bethanidine sulfate administered orally is practically without such effect, and that this preparation is now undergoing a limited clinical trial. Perhaps more logical would be the development of a combined and rapid-acting alpha and beta receptor blocking agent. Such a preparation would have no effect on blood pressure, and by virtue of its action on alpha receptors might prevent the occurrence of sympathetic vasoconstriction. The feasibility of this approach must, however, await further investigation.

J. Grayson, D.Sc., M.D.
Department of Physiology
University of Ibadan
Ibadan, Nigeria

REFERENCES

1. Spalteholtz, W.: Die Arterien der Herzwand, Leipzig, 1924, S. Hirzel.
2. Blumgart, H. L., and Zoll, P. M.: Pathological physiology of angina pectoris and acute myocardial infarction, *In* Symposium on Coronary Heart Disease, American Heart Association, 2:154, 1961.
3. Estes, E. H., Entman, M. L., Dixon, H. B., Hackel, D. B., and Durham, N. C.: The vascular supply of the left ventricular wall, Am. Heart J. 71:58, 1966.
4. Gombrl, Z.: Demonstration at necropsy of interarterial coronary anastomoses in human hearts, Ztschr. Kreislaufforsch. 54:1181, 1965.
5. Fulton, W. F. M.: Anastomotic enlargement and ischaemic myocardial damage, Brit. Heart J. 26:1, 1964.
6. Fulton, W. F. M.: The dynamic factor in enlargement of coronary arterial anastomoses and paradoxical changes in the subendocardial plexus, Brit. Heart J. 26:39, 1964.
7. Rodriguez, F. L., and Robins, S. L.: Postmortem angiographic studies on coronary arterial circulation. Intercoronary anastomoses in adult human hearts, Am. Heart J. 70:348, 1965.
8. Gregg, D. E.: Coronary circulation in health and disease, Philadelphia, 1950, Lea & Febiger.
9. Gregg, D. E., and Fisher, L. C.: Blood supply to the heart, *In* Handbook of physiology, Section 2, Circulation, Vol. 2, p. 1517, Baltimore, 1963, Williams & Wilkins.

10. Krug, A., Rochement, W. and Korb, G.: Blood supply t the myocardi m after temporary coronary occlusion, Circulation Res. 19:57 1966.
11. LeRoy G. W and Snider S. S. The sudden death of patients with few symptoms of heart disease, J.A.M.A. 117:2019 1941
12. Dawes, G. S. Studies on veratrum alkaloids receptor areas in coronary arteries and elsewhere as revealed by the use of veratrin J Pharmacol. & Exper Therap 89:325 1947
13. Dawes, G. S. nd Comroe, J H Chemoreflexes from the heart and l ngs, Physiol. Rev 34 167 1954.
14. Lebedinskii, A. V Medvedev v I and Pelmer I A. Importance of coronary spasm in the pathogenesis of coronary insufficiency Sukhumi, Nauk. N uk. Akad. Med U.S.S.R p 32, 1954.
15. Lapin, B. A. Pathogenesis of myocardial infarction, Bull. Exper Biol. & Med. (U.S.S.R — English translation) 40 19 1955.
16. Opdyke D F and Selkurt, E. E. A study of alleged intercoronary reflexes following coronary occlusion, Am. Heart J 36 73, 1948.
17. Way H. H., Frank, C. W Kanter D M and Wegria, R. Experimental studies on intercoronary reflexes, Circulation Res. 5:91, 1957
18. West, J W Kobayashi, T and Anderson, F S. Effects of selective coronary embolization on coronary blood flow and coronary sinus venous blood oxygen saturation in dogs with special reference t coronary reflexes, Circulation Res. 10 722, 1962.
19. Gorman, S V Swenson, E., and Jones, M. Intercoronary reflex. demonstration by coronary ngiography Circulation Res. 10 739 1962.
20. Kiese, M and Lange, G. Calorimetrische Messung der durchbl tung des Herzmuskels, Arch. exper Path. u. Pharmakol. 231 149 1957
21. Grayson, J and Mendel, D Myocardial blood flow in the rabbit, Am J Physiol. 200 968 1961.
22. Grayson, J and Parratt, J R. A species comparison of the effects of changing perfusion pressure on blood flow and metabolic heat production in the myocardium, J Physiol. I press.
23. Grayson, J and Lapin B. A Observations on the mechanisms of infarction in the dog after experimental occlusion of the coronary artery Lancet 1 1284 1966.
24. Boura, A. L. A., nd Green, A. F Adrenergic neurone blockade and other acute effects caused by n-benzyl-o dimethylguanidine and its ortho-chloro derivative, Brit J Pharmacol. 20:36, 1963.
25. Alleyne, G. A. O Dickinson, C J Dornhorst, A. C., Fulton, R. M., Green, K. G. Hill, I. D Hurst, P Laurence, D R., Pilkington T Prichard, B. N C., Robinson, B. and Rosenheim, M L. Effect of pronethalol in angina pectoris, Brit. M. J 2 1226, 1963.
26. Entman, M Hackel, D B. Martin, A., Mikat, E., and Chang, J Alteration of the cardiac lesions of haemorrhagic shock by β sympathetic blockade, Fed. Proc. 24:586, 1965.
27. Baroldi, G. Acut coronary occlusion as cause of myocardial infarct and sudden coronary heart death, Am. J Cardiol. 16:859 1965.

Letter to the Editor

The role of hydralazine in the prevention of significant bacteriuria and pyuria in the hypertensive man

To the Editor

It has been demonstrated in the rat that intravenous injection of hydralazine is associated with decrease in medullary sodium concentration and an increase in medullary electrical resistance[1,2] without any significant change in either parameter in the renal cortex.[3] Similar results have been also obtained in the dog. The increase in electrical resistance of the renal medulla implies that, in addition to the reduction of medullary sodium, there is also a decrease in medullary osmolality. Since alterations in medullary sodium concentration are inversely related to medullary blood flow[3] and since hydralazine is known to increase total renal blood flow, these changes in sodium concentration and electrical resistance were attributed to an increase in medullary blood flow.[4]

Recently it has been demonstrated that depression of phagocytosis occurs by solutes in concentrations found in the kidney and urine.[11] Most recent experiments in the rat have shown that, following water diuresis (which is also known to increase medullary blood flow),[12,24] a reduction in medullary osmolality and sodium content occurs. Such change of the medullary tissue from hypertonic to isotonic or nearly isotonic, may result in an increase in leukocyte migration and phagocytosis, which in turn, may prevent the development of Candida and staphylococcus-induced pyelonephritis.

In contrast, in the animals which were not subjected to water diuresis prior to inoculation with these pathogens, in the majority of the cases the prevention of pyelonephritis was not possible. In addition to the inhibition of phagocytosis by hypertonic saline solutions,[25] there is evidence that such hypertonicity may also inhibit the activity of complement. Furthermore, hypertonic solutions are known to preserve protoplasts.[27]

In view of the fact that reduction in medullary sodium concentration and osmolality also occurs following administration of hydralazine, it was assumed that this agent may enhance leukocyte migration and phagocytosis. In order to determine whether the chronic use of hydralazine in hypertensive patients may play such a protective role, a retrospective clinical study was undertaken in 75 randomly picked hypertensive patients. Except for the presence or absence of hydralazine in their antihypertensive armamentarium, the patients were otherwise unselected.

The series consisted of two groups. One group was composed of 40 patients who were treated with various antihypertensive drugs plus hydralazine and the other group included 35 patients who received other hypotensive agents but not hydralazine. The degree of bacteriuria and pyuria was determined by repeated urinalyses, and also urine cultures were done when indicated.

The results are summarized in Table I. Significant bacteriuria (3+ and 4+ bacteria per high-power field in at least one specimen) and pyuria (more than 5 pus cells per high-power field in at least one specimen) were much more prevalent among the nonhydralazine than among the hydralazine treated group. In contrast, the number of urinalyses free of bacteria and with no significant pyuria was much higher in the hydralazine than in the nonhydralazine treated group.

These observations, coupled with our previous findings in animals and the studies of others, suggest the following: (1) The incidence of significant bacteriuria and pyuria in hypertensive patients who do not receive hydralazine is threefold to fourfold higher than in those who do receive hydralazine. (2) The addition of hydralazine in the antihypertensive regimen may decrease the susceptibility of the renal medulla to infections probably by increasing medullary blood flow and reducing medullary sodium concentration and osmolality. (3) The degree of bacteriuria and pyuria probably reflects the degree of pyelonephritic process in the renal medulla which is influenced by the migration of leukocytes and phagocytosis which, in turn, is dependent on medullary blood flow and medullary tonicity.

Under normal conditions, because of the countercurrent concentrating and diffusion exchange mechanisms,[28] the renal medulla is hypertonic, as compared to the cortex. The medullary hypertonicity and/or the reduction of medullary blood flow may be responsible for the susceptibility of the renal medulla to infections. It has been shown in the rat that, following intravenous injection of vasopressors, an increase above the control occurs in medullary sodium concentration.[3] This increase in medullary tonicity has been attributed to a decrease in medullary blood flow. Since human hypertension is associated with a decrease in renal blood flow,[29,30] it is conceivable that a similar increase in medullary sodium concentration and osmolality also occurs in the hypertensive man. Such an increase in medullary hypertonicity and/or decrease in medullary blood flow may explain why the prevalence of pyelonephritis is much higher among hypertensives

Table I. Correlation of bacteriuria, pyuria, and urine cultures between hydralazine and non hydralazine treated hypertensive patients

Patient groups	Number of patients	U analysis			Bacteriuria					Pyuria	Urine cultures	
		Total number	Men	Range	0	1+	2+	3+	4+	More than 5 WBC per high-power field	Number done	Number positive
Nonhydralazine treated	35	274	7	1-41	119	83	35	16	21	19	19	11
Hydralazine treated	40	309	7	2-55	231	68	5	4	1	7	13	0

than among normotensive individuals. Similarly, the high incidence of significant bacteriuria and pyuria seen in the presence of renal artery stenosis[8] could be attributed to reduced medullary blood flow and increased medullary sodium concentration. An increase in medullary sodium concentration above the control level has been also seen in rats[9] and dogs during hydropenia. This increase in medullary sodium concentration may be due to reduction in medullary blood flow as a result of an increased ADH activity, which is known to decrease medullary blood flow.[10] It is of interest to note that the effect of hydralazine in reducing medullary sodium concentration is more pronounced in the hydropenic than in the nonhydropenic animal. Similarly, it is speculated that hydralazine may be more effective in reducing medullary osmolality in the hypertensive man than in the normotensive man. Nevertheless, in the presence of chronic recurrent pyelonephritis, regardless of whether the patient is hypertensive or normotensive, the use of small doses of hydralazine may be beneficial in preventing exacerbations. In view of the fact that the hypotensive effect of hydralazine when it is given alone is mild, this drug may be used in small doses by hypertensive and normotensive patients alike. Another drug which might be potentially effective in preventing pyelonephritis is α-methyldopa. It has been learned that, following the administration of this agent, renal blood flow may either increase[11] or remain unchanged.[12] An increase in renal blood flow due to any drug could have an effect similar to that of hydralazine. However, α-methyldopa is a potent antihypertensive agent and should be used with caution and only in hypertensive patients.

In summary, the conclusion is that hydralazine may reduce the incidence of significant bacteriuria and pyuria and presumably may prevent the occurrence or the recurrence of pyelonephritis in hypertensive and perhaps in normotensive patients. In view of our own experimental work and the recent studies of others, it is suggested that the beneficial effect of hydralazine is probably due to an increase in medullary blood flow and reduction in medullary sodium concentration and osmolality which, in turn, may enhance the migration of leukocytes and phagocytosis in the renal medulla.

Ignatius J. Vondoukas, M.D.
Division of Hypertension
Department of Medicine
Henry Ford Hospital
Detroit, Mich. 4820

REFERENCES

1. Brandt, J. L., and Vondoukas, I. J.: Effect of vasoconstrictors and dilators on renal tissue sodium concentration, Fed. Proc. 23:363, 1964.
2. Vondoukas, I. J., Nelson, C. V., Rand, P. W., Dienst, S. D., and Chatterjee, M.: Renal tissue electrical resistance under control conditions and following administration of hydralazine. Presented at the 37th Scientific Sessions of the American Heart Association in Atlantic City, N. J., October, 1964. Circulation 30:174, 1964 (Abstract) Suppl. No. III.
3. Vondoukas, I. J., and Nelson, C. V.: Sodium concentration and electrical resistance of renal tissue. Am. Heart J. 69:124, 1965.
4. Vondoukas, I. J.: Unpublished data.
5. Berliner, R. W., Levinsky, N. G., Davidson, D. G., and Eden, M.: Dilution and concentration of the urine and the action of the antidiuretic hormone. Am. J. Med. 24:730, 1958.
6. Carriere, S.: Influence of medullary ... on the osmotic gradient of the kidney. Presented at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May, 1966. Clin. Res. 14:373, 1966.
7. Reubi, F. C.: Renal hyperemia induced in man by a new Phthalazine derivative. Proc. Soc. Exper. Biol. & Med. 73:102, 1950.
8. Moyer, J. H., Handley, C. A., and Huggins, R. A.: Some pharmacodynamic effects of 1-hydrazinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. J. Pharmacol. & Exper. Therap. 103:368, 1951.
9. Wilkinson, E. L., Backman, H., and Hecht,

H H Cardiovascula nd renal adjustment t h potensive agent (L h drazinophthala ne Ciba BA 5968 Apresoline) J Cl I vest 31:872, 1952

10. Chernew I nd Braude A J Depression of phagocytosis b sol tes in concentr t ons found in the kidney and urine, J Cl I est 41 1945 1962

11 Andriole V T and Epstein F H Prevention of pyelonephritis by w ter d uresis I videnc for the role of med llary h pertonicit promoting renal fection J Clin. I vest 44 73, 1965

12 Andriole V T Acceler tion of the inflammatory response of the renal med lla by w ter d uresis J Clin I vest 45:847 1966.

13 Ihur K Deetjen P nd K amer K Hamod namik des Nierenmark II M tteilung W hselbezieh ng zwishen sc larem nd bularem Gegenstrom y tem bei arteriellen Druck teiger ngen, Wasserd uresis nd osm tisch D res s, Pflugers Arch Ges Ph siol 270:270 1960

14 Ullrich K J Kramer K nd Boylan, J W Presen t knowledge of he cou tercurrent stem he m mm lia kidney Prog Ca diov Dis 3:395 1961

15 Hamburger H J Ph k lisch—Chemisch U tersungen uber l h g sysen Wiesbaden 1912

16. Kal t F A nd M yer M M Experi ient I laum nochemistry Spri gfield, Ill., 1948, Charles C Thomas, p 105

17 Br ude A I Siemienski, J nd Jacobs, I Protoplast formation I h man urine Tr A Am Physicians 74:234 1961

18 Sm th H W The kidney structure and f nc tion In he lth nd disease, New York 1951 Oxford U iversity Press.

19 Wilkins, R W Physiological investigations of essential hypertension in man A symposium on essential h pertension, Boston, 1951 Wright and Potter Pri ting Co., p. 94

20 Reubi F C The lat effect of hypotensive drug therapy on renal functions of patient with essential hypertension n Essential hy pertension, an international symposium, edited by K. D Bock nd I T Cottier Berlin 1960, Springer Verlag p 317

21 Voudoukis, I J L published data.

22 Onesti, G., Brest A. N Novack, P Kasparian, H nd Moyer J H Pharmacodynamic effects of lpha-methyldopa in hypertensive subjects, Am Hea t J 67:32 1964

23. Sa nerstedt, R Boja, G Varnauskas, F nd Werko, L Alpha-methyldopa in arterial hypertension. Clinical, renal and hemodynamic tudies, Acta Med. Scandinav 173:53 1963.

Book reviews

ANESTHESIA FOR OPEN HEART SURGERY Compiled and edited by Lillian E. Fredericks M.D. and Dryden P Morse M.D. Springfield, Ill 1966 Charles C Thomas, Publisher 80 pages. Price $3.50.

This 75-page volume consists of 17 sections presumably chapters, 3 or 4 pages in length and each by different contributor Each of these is an excerpt of symposium commemorating two decades of cooperative endeavors in the fields of anesthesia and open-heart surgery in Philadelphia, where cardiac surgery was pioneered by Dr Charles Bailey and Dr John Gibbon The intention of the editors in compiling and publishing the symposium is "t acquaint anesthesiologists and cardiac surgeons with some of the practices and desires of their colleagues across the ether screen The excerpts are abbreviations of papers presented at the symposium by group of twenty cardiovascular and thoracic surgeons and anesthesiologists in Philadelphia. Among the subject included are the choice of anesthesia, preparation for anesthesia, monitoring, hypotension, blood loss, blood procurement, coagulation problems, acid-base balance disturbances, pulmonary function and the use of ventilators, etc

The coverage of these topics is superficial, casual, and general. They are deficient in both breadth and depth. The editors state that, in the interest of brevity the taped transcript of the proceedings underwent considerable editing but they hope that the natural spontaneity and flavor of the spoken words of the distinguished contributors has not been lost Unfortunately the hopes of the editors have not been realized. The reviewer is familiar with the writings of some of the contributors and participants and notes that the contributions in this volume are not of the caliber and quality of other previously published writings.

Continuity is lacking The subject matter in one chapter does not blend with that in the next or follow in logical sequence. Important aspects of cardiac surgery and anesthesia are slighted or omitted whereas matters of minor importance are emphasized. It is doubtful whether well seasoned cardiac surgeon or an anesthesiologist who has been reasonably exposed to open-heart surgery will learn much from this volume, and the cardiologist or internist who would like to become acquainted with the problems of anesthesia and management of the patient during open-heart surgery will not be able to gain such information from this volume The volume will be of little value to the trainee in anesthesiology or cardiac surgery since it lacks important details of basic nature. The methods and procedures described by the authors are their personal preferences, presented in dogmatic fashion, and leave the reader with the impression that there is no other way to manage a particular situation The reviewer wonders why the editors place so much emphasis on brevity when possibly few additional pages of subject matter would have resulted in more useful volume on the subject.

DIE PROGNOSE DER ESSENTIELLEN HYPERTONIE By Prof Dr K. Kuhns and Dr Med O Brahms, Darmstadt, 1966, Dietrich Steinkopff Verlag 119 pages.

This is review of 4,329 patients, treated at the University clinic of Göttingen in the years 1950 to 1955, with follow-up during the years 1956 to 1959 The material is treated with special reference to the influence of age, sex, body weight, height of blood pressure, occupation, heredity, findings on heart examination, kidney function ophthalmoscopic findings and symptoms. The influence of these factors on the prognosis of hypertension is evaluated. Of special interest is the last chapter on the influence of drug therapy on the prognosis. Up to 1955 the following drugs were used sedatives, rauwolfia-alkaloids, hydralazine, and ganglionic-blocking agents. Thus, there is no evaluation of newer drugs, such as the thiazides, Aldomet, and guanethidine. In this study there was distinct improvement in prognosis after rauwolfia. This book is, in so far as it goes, critical review of factors known to influence the prognosis of essential hypertension.

Books received

MODERN TREATMENT Vol 3 No 6 November 1966 (1) Treatment of Collagen Diseases, by Clarence F Rupe. (2) Treatment of Adrenal Disorders, by Don H Nelson New York 1966, Hoeber Medical Division, Harper and Row 1,400 pages per year Price $16 per ea

ON ... HEALTH Free copies can be obtained from the U S Department of Health, Education and Welfare U S Public Health Service

P... TOWARDS ... ANATOMO... Polskie Towarzystwo Anatomopatologiczne; Bialystok 24-26 wrzesnia, 1964, Supplement do patologii Polskiej 1/1965 Bialy ... 1965 696 pages.

Announcements

THE IV PANAMERICAN CONGRESS OF RHEUMATOLOGY will be held in Mexico City October 22-26, 1967

For further information, write General Secretary Dr Gábor Kátona Av. Cuauhtémoc 300, México 7 D.F México.

THE 8TH INTERNATIONAL COLLOQUIUM ON VECTORCARDIOGRAPHY arranged by the 1st Medical Clinic of the University of Vienna in cooperation with the Medical Academy for Postgraduate Studies of Vienna, will be conducted in Vienna, Sept 18-21 1967

The Colloquium will be under the scientific direction of Prof Dr R Wenger The following subjects will be on the agenda (1) Electrophysiologic fundamentals, especially relative to the distribution of surface potentials on the thorax. (2) Problems of methodology and standardization. (3) Vectorcardiography at the clinical hospital. (4) Data processing in electrovectorcardiography

Enquiries should be directed to Prof Dr R. Wenger Scientific Director 8th International Colloquium on V.C.G., Stadiongasse 6-8, A 1010 Vienna, Austria (tel. 42-61-87)

The NOVENA ASAMBLEA MÉDICA DE MÉXICO will take place in Guadalajara, Mexico November 21 through 25 1967 This meeting, one of the largest in Mexico is sponsored by the University of Guadalajara.

American Heart Journal

May 1967 Volume 73 Number 5

Editorial

Blockpnea on effort in emphysematous patients—A diagnostic challenge

Henri Chevalier, M.D.
Paris, France

The diagnosis of angina pectoris on effort in its classic form and even in its atypical aspects does not raise real difficulties for the experienced cardiologist. Only in a very small percentage of cases, which remain doubtful after keen clinical scrutiny, does recourse to supplementary investigations appear to be legitimate and necessary. These methods (electrocardiographic exercise tests, coronary sinus blood analyses, cine-coronary arteriography) aim *to confirm suspected coronary insufficiency*—this latter term is used in its strict pathophysiologic sense. They can help, although all of them do have their pitfalls and drawbacks.

In contrast to typical angina pectoris there is a variant form, a painless equivalent, which in limited situations can present the most astute clinician with a real diagnostic dilemma. This variant was accurately described by Louis Gallavardin[1] as early as 1924, and in subsequent papers. In 1933 he coined the word "blockpnea" on effort for it. Strangely enough, this prominent equivalent expression of cardiac pain seems to have gained little recognition in the American medical literature. The leading textbooks on heart diseases do not even mention its existence in their long paragraphs devoted to detailed descriptions of angina pectoris. However, this variant is by no means a rarity, and when well identified it leads straight to the correct diagnosis of coronary insufficiency. In brief, the symptom appears in the same context as true anginal pain, especially under the direct influence of walking. It consists not in a banal tachypnea or a pain but in an increasingly agonizing feeling of *respiration bouchée* (blocked *respiration*, suffocation) which forces the patient to stop and stand still, for otherwise he feels that he will fall down and die. The respiratory blockade and apnea subside little by little while thoracic movements resume *with no wheezing* or cough, and walking is possible again. Sublingual nitroglycerin relieves the blockade in a matter of seconds, as it does with anginal pain.

Anginal blockpnea should not be confused either with plain polypnea or with that intense respiratory embarrassment occasionally accompanied by substernal pain which, in so-called idiopathic pulmonary hypertension, is observed on walking. Almost always the clinical, roentgenologic, and electrocardiographic abnormal

Received for publication Feb. 19, 1966.
*Consultant Cardiologist, 111 Boulevard Malesherbes, Paris 17, France.

ities render the diagnosis of primary pulmonary hypertension relatively easy. Distinction may prove to be somewhat more difficult with bronchial asthma when bronchospasm occurs under the influence of effort. But asthma on effort generally coexists with typical attacks at rest. In addition, wheezing takes place when bronchospasm yields, a characteristic hallmark of bronchial asthma which is strikingly lacking in anginal blockpnea. In uncertain cases, nitroglycerin and isoproterenol tests can elegantly help to settle the question. In fact, the one and only alternate diagnosis that can challenge the clinician's sagacity is diffuse obstructive pulmonary emphysema. Of course, tachypnea, not blockpnea, is the symptom commonly induced by effort in the vast majority of patients with emphysema. However, in a significant but small group of patients, especially in those whose respiratory reserve has been critically curtailed, simple walking triggers, instead of polypnea, a sensation of suffocation that is closely like anginal blockpnea in every respect, including absence of wheezing on resumption of respiration. (The mechanism of this emphysematous blockpnea on effort remains conjectural.) In such circumstances, diagnosis will be either very easy or desperately difficult, according to whether pulmonary function proves to be normal or not. Thus two possibilities may arise.

1. If there is no evidence whatsoever of respiratory impairment in the patient in question, then the diagnosis of anginal blockpnea is unequivocally settled, and there is no reason to perform further special investigations to establish coronary insufficiency.

2. In contrast, when blockpnea on effort is observed in a patient—often middle aged or elderly—who is obviously afflicted with severe respiratory deficiency from diffuse obstructive emphysema, the blockpnea gives rise to the following diagnostic dilemma. Is the blockpnea related to the evident existing emphysema or is it an anginal variant unveiling ischemic heart disease now *superimposed* upon bronchopneumopathy of long duration? Here lies the crux of the matter, and the distinction is far from an academic one. Emphysematous blockpnea is not fatal, whereas anginal blockpnea carries the ever-present threat of sudden death. Therefore, insofar as prognostic implications are concerned, it behooves the cardiologist to strive to solve the enigma. On purely clinical grounds I know of no clues that could help in reaching the correct answer, except perhaps when ancillary factors do to a degree make more plausible a suspicion of ischemic heart disease (diabetes, systemic hypertension, obesity, eloquent atherosclerotic heredity). Pharmacodynamic tests (nitroglycerin and isoproterenol), in my own experience, give rather unreliable responses in this peculiar situation. Roentgenology is of no help, for it simply demonstrates signs of already evident emphysema. Electrocardiograms at rest can be helpful if they disclose changes that are diagnostic of coronary artery disease (i.e., myocardial infarction) or at least strongly suggestive of myocardial ischemia. Too often the electrocardiograms show nothing but signs of pulmonary emphysema. Thus, in an effort to clear away uncertainties, one feels naturally inclined to call upon the more elaborate techniques, the use of which has been so ardently advocated for establishing unquestionable evidence of (arteriosclerotic) coronary disease. Let us consider each of them.

a. Exercise electrocardiographic tests, despite widespread use, still remain of debatable value, even in subjects young and free from pulmonary impairment, for many factors beside cellular ischemia can intervene to disturb ventricular electrogenesis and hence make for equivocal responses. The use of these tests appears to be simply unrealistic in patients whose respiratory reserve is so frail. Moreover, the results of the tests would be highly questionable because of exertionally produced acute arterial unsaturation in the coronary bed as well as in other areas.

b. The same objection holds for measurements of *arteriovenous oxygen difference* after exercise in the coronary sinus blood, and it seems to be very probable that the determination of lactate in the coronary venous blood—a physiologic method for the estimation of anaerobic metabolism induced by inadequate arterial flow, full

of promise but still in the experimental stage—would meet similar limitations in the emphysematous patient.

c. Thus to establish coronary artery disease it would seem to be logical to resort to visualization of the arterial tree through *coronary arteriography* or better *cine coronary arteriography*. Unfortunately in these fragile patients so formidable a radiologic examination raises quasi prohibitive risks. Furthermore, although these techniques offer a more or less accurate and extensive anatomic picture of the coronary arterial tree, they by no means give any reliable information about the functional state of the coronary system and of coronary *flow* as a whole or in its various segments. Lastly coronary arteriography cannot reveal what happens in the intimacy of myocardial cell metabolism. Parenthetically, recent experience gained from renal arteriography with respect to renovascular hypertension should temper overenthusiasm about extrapolating from vascular *morphology* to arterial *flow* and cellular metabolism in any parenchyme. Bitter deception and confusion have eventually come from the naive hopes stemming from initial contrast studies of renal arteries. I presume that a similar swing of the pendulum will soon be observed with cine coronary arteriography applied to the evaluation of coronary flow.

d. More acceptable and fitting for that category of handicapped patients under discussion would appear to be those various methods of determination of coronary flow that avoid catheterization of the coronary sinus by using external (precordial) counting with radioactive rubidium.[6, 7] Unfortunately these techniques, although extremely promising, are still in the developmental stage and presently lack accuracy.

In the final analysis, we are obliged to confess that at the present time there are no clinical techniques of investigation which are dependable and safe enough to provide us with a clear-cut answer to this diagnostic enigma. When blockpnea on effort appears in a notoriously emphysematous patient, is that peculiar symptom related solely to the long-known respiratory deficiency, or does it reflect a coexistent independent ischemic heart disease now superimposed upon antecedent pulmonary emphysema?

As a meager consolation from our diagnostic failure, we do know at least which therapeutic agent is the most effective for the relief of these crippled patients. It is aminophylline given in large doses by various routes (oral, rectal, intramuscular, and in aerosols), for this drug is endowed with protean precious capabilities since it improves, at the same time, coronary flow, lung function, and pulmonary blood flow through the lowering of arterial resistance. It does, to a modest extent, benefit these patients.

In summary, when blockpnea on effort—a painless variant of angina pectoris—develops in a patient suffering from pulmonary emphysema, it seems to be practically impossible to decide whether this symptom results from the pulmonary insufficiency which is obviously present or whether it is due to an occult concomitant coronary insufficiency. Unfortunately, at the present time there are no additional methods of investigation that are suitable for clarifying this baffling diagnostic challenge.

REFERENCES

1. Gallavardin, L.: Y a-t-il un équivalent non douloureux de l'angine de poitrine d'effort? Lyon Méd. 2:345, 1924.
2. Gallavardin, L.: Les syndromes d'effort dans les affections cardioaortiques. J. méd. Lyon 14:539, 1933.
3. Friesinger, G., Lilker, I., Biern, R., and Mason, R.: Vasoregulatory asthenia: A cause for false-positive exercise electrocardiograms. (Abstract) Suppl. II, Circulation 28:90, 1963.
4. Scheuer, J., and Brachfeld, N.: Coronary insufficiency: Relations between hemodynamic, electrical and biochemical parameters. Circulation Res. 18:178, 1966.
5. Zimmerman, H. A., and Demany, M. A.: Coronary artery visualization and coronary surgery—A word of caution. (Editorial) AM. HEART J. 72:725, 1966.
6. Love, W., and Burch, G.: Study in dogs of methods suitable for estimating the rate of myocardial uptake of Rb^{86} in man and the effect of l-norepinephrine on Rb^{86} uptake. J. Clin. Invest. 36:468, 1957.
7. Donato, L., Bartolomei, G., Federighi, G., and Torreggiani, G.: Measurement of coronary blood flow by external counting with radioactive rubidium. Circulation 33:708, 1966.

Clinical communications

The course of pulmonary embolism

Norman D. Poe, M.D.
Leonard A. Swanson, M.D.
Earl K. Dore, M.D.
George V. Taplin, M.D.
Los Angeles, Calif.

Although pulmonary embolism is now recognized in hospital practice as a major acute chest disease, relatively little is known of its natural course, particularly the recovery phase. Some large emboli have been demonstrated by repeated pulmonary angiographic studies to resolve in 1 to 4 weeks. However, the usual rates of recovery from emboli of different sizes and types have not been determined. Such information is needed in order to evaluate thrombolytic and anticoagulant agents in the therapy of this disorder and to reassess the indications for surgical intervention.

Lung scanning after the intravenous injection of macroaggregated radioalbumin (RAMA) provides a safe and reliable method for measuring the changing arterial perfusion during recovery from pulmonary embolism.[7] The procedure may be repeated as often as necessary, and it is our opinion, based on experience with 400 patients suspected of having pulmonary embolism, that lung scanning is the most convenient and probably the most sensitive method now available for this purpose.

This paper describes the selection and classification of the patients studied and presents the results of lung perfusion scans from 20 individuals with uncomplicated pulmonary embolism who were examined at frequent intervals throughout the course of the disease. The differences in recovery rates in man are discussed in relationship to the possible mechanisms involved and to the findings of other investigators in experimental pulmonary embolism.

Clinical material and management of patients

The patients included 8 male and 11 female adults ranging in age from 20 to 81 and one 4-year-old boy. The diagnosis of pulmonary embolism was based on the assessment of clinical, laboratory, roentgenographic, and radioisotope perfusion scan findings. The diagnosis was further confirmed in 7 individuals by pulmonary arteriography. Patients with pneumonitis, uncompensated congestive heart failure, emphysema, and pleural effusion were excluded because these disorders can also cause regional pulmonary ischemia.

From the Laboratory of Nuclear Medicine and Radiation Biology, School of Medicine, University of California at Los Angeles, and the Los Angeles County Harbor General Hospital, Torrance, and the Memorial Hospital of Long Beach.

These studies were supported by Contract AT(04-1)-GEN 12 between the U. S. Atomic Energy Commission and the University of California at Los Angeles.
Received for publication June 20, 1968.

Address: Laboratory of Nuclear Medicine and Radiation Biology, School of Medicine, University of California at Los Angeles, 900 Veteran Ave., Los Angeles, Calif., 90024.

Among the 19 adults, 10 had evidence of pre-existing thrombophlebitis, 2 had varicose veins, 1 was immobilized because of a knee fracture, 4 had compensated congestive failure, and the other 2 had no detectable sources of emboli. The child had a bacterial endocarditis at the site of a ventricular septal defect, and this was suspected clinically to be the origin of a septic embolus.

All 20 patients received anticoagulant therapy. The child was maintained for a short time on heparin alone, and 2 of the adults were given oral anticoagulants only. The other 17 were started on intravenous or subcutaneous heparin immediately after the diagnosis was established and then maintained on oral anticoagulants for the duration of the study. During the treatment with heparin an attempt was made to keep the clotting time at least twice normal at all times. With oral anticoagulation measurements of prothrombin time were used to evaluate and modify the treatment regimen. Control of such treatment was not entirely satisfactory, particularly in patients who left the hospital during the follow-up period. Inasmuch as the medical care of each patient was not directed by a single physician but rather by the resident staff of several services in the hospital or by private physicians, no standard program of anticoagulation was maintained.

Test agent, equipment, and scanning procedure

Radioalbumin macroaggregates (obtained mainly from one radiopharmaceutical manufacturer*) were administered in doses of 180 to 300 μc in the adult and 80 μc in the child. Five milliliters of 10 per cent sodium perchlorate or three drops of a saturated solution of potassium iodide was given orally preceding all injections of RAMA in order to minimize exposure of the thyroid to radiation.

The injection of tracer was made routinely with the patient in the sitting position. The scan was performed immediately thereafter with the patient in the prone position in order to obtain a posterior view of the lungs. When patients were unable to lie prone, an anterior scan was performed. Either one or both lateral views were then obtained as indicated from the results of the initial procedure. Each view of the chest required 15 to 20 minutes with scanning rates of 100 to 120 cm. per minute. Most of the scans were made using a Picker Magnascanner Model III, which had a 3-inch diameter crystal and 7-hole tapered hexagonal collimator with a 2-inch focus. Chest x-ray films (PA or AP) were taken with the patient in the same position in which the scan was performed.

A minimum of 3 but as many as 8 scans and roentgenograms were made in each patient during the course of his disease. The duration of the study varied in each patient and ranged from 7 days to 16 months from the date of the first examination. The embolic lesions were classified as lobar, segmental, or subsegmental according to the size, shape, and location of the areas of ischemia found in the lung scan images.

Results

The recovery times, classification of the emboli, duration of follow-up, and predisposing conditions of the 20 patients studied are presented in Table I. The recovery time is the interval between the initial scan and the scan demonstrating restored blood flow. If the onset of the acute illness preceded the initial scan by more than 48 hours, the date of the first symptoms was used.

Only one patient had evidence of a single embolus; the remainder had multiple lesions. Nine had occlusion of one or two lobar arteries (Fig. 1). In 6 of these the scans demonstrated complete restoration of blood flow within 4 to 17 days, whereas recovery in 2 other patients occurred at 4 weeks in one and at 6 weeks in the other. The child with the septic embolus had no flow of blood to the entire right lower and middle lobes with x-ray evidence of infarction in one segment of the lower lobe. Unlike the rapid resolution in adults with noninfected emboli, no improvement occurred during 16 months of observation (Fig. 2).

Fifteen patients had one

*E. R. Squibb and Sons, Radiopharmaceutical Division, New York, N. Y.

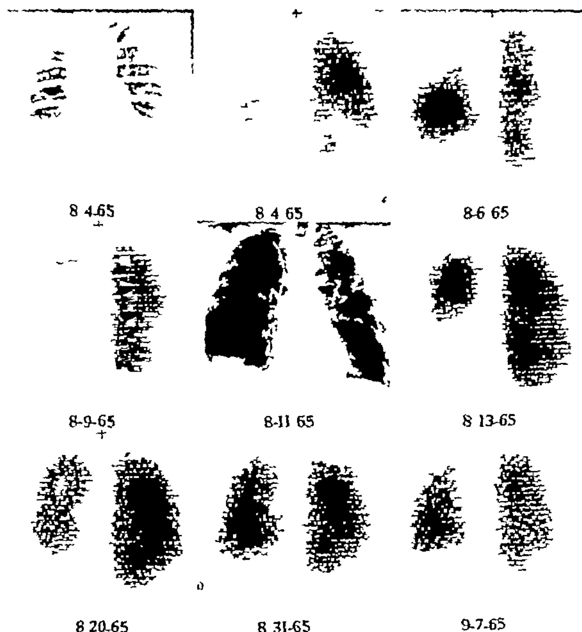


Fig 1 Case No 8 (L L) Blood flow to the right upper lobe is gradually restored over a 9-day period. More rapid return of flow to the right lower lobe is seen after the initial embolus but a prolonged course follows the recurrent embolus Numerous segmental and subsegmental emboli are seen in the left lung.

mental emboli Half showed complete recovery at the same rates as those with the lobar lesions but in the others there was little improvement for 2 to 4 months or longer (Figs. 1 and 3) In one case a defect persisted for 14 months.

Subsegmental emboli were identified in only 6 patients. Recovery times varied from 3 days to 6 weeks (Fig 4) Emboli which produce areas of ischemia smaller than 2 to 3 cm. in d[illegible] are not detectable with the scann[illegible] ment and proced[illegible]

No[illegible] led

and u[illegible]

dence o[illegible]

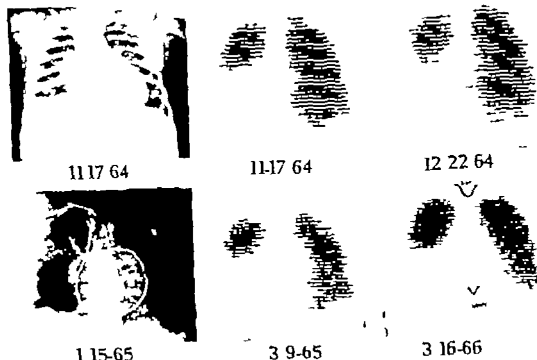


Fig. 2. Case No. 13 (J. N.). Unlike rapid resolution of uncomplicated lobar emboli, no return of blood flow is seen 16 months after a septic embolus to the right lower lobe.

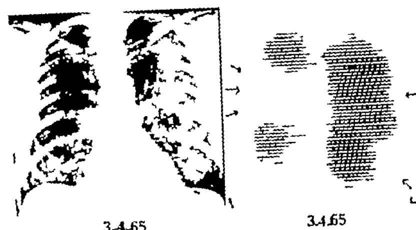
than 48 hours after adequate heparinization.

Discussion

The true incidence of pulmonary embolism in the general population is not known nor are accurate mortality rates available but as many as 47,000 deaths per year in this country have been attributed solely to this disease.[4] These deaths probably represent the relatively few major embolic episodes which comprise only a small fraction of the total incidence. On the basis of gross examination at autopsy pulmonary embolism has been estimated to have a frequency varying between 10 and 30 per cent. With more careful histopathologic examination of the lungs, a much higher incidence has now been demonstrated. Freiman and associates report emboli in 64 per cent of 61 consecutive autopsies in adults. Many were minute and others were identifiable only by the presence of fibrous bands and webs. Since only a small percentage of old emboli leave these telltale signs, the true incidence may be even higher. Thus, it is reasonable to postulate that pulmonary embolism may occur in nearly everyone at one time or another and that the disease as now recognized clinically probably represents only a tiny segment of the broad spectrum of this disorder.

Experimental embolism studies. Marshall has recently reviewed the literature on experimental pulmonary embolism and no attempt is made here to cover the subject. However certain studies are particularly applicable to the course of pulmonary embolism and are mentioned briefly.

Small fresh autologous emboli are cleared so rapidly in dogs that little or no evidence is detectable 5 to 13 days later even on careful histologic examination. As the number of injected emboli is increased the probability of finding them soon after injection is considerably enhanced although the numbers found decrease progressively from day to day during the first week. Histologically, retrac-



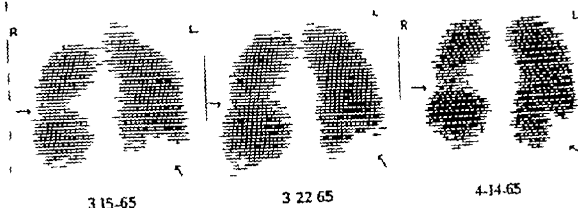


Fig. 3. Case No. 17 (C. R.). Rapid improvement is seen in some segmental lesions, whereas others show no change in 6 weeks.

tion of the few remaining thrombi begins within 3 to 4 days. Adherence to the arterial wall becomes evident by 4 to 5 days and is followed by organization and fibrosis with further reduction in the size of the clot. Within 4 to 6 weeks the clots are usually completely resolved and manifest themselves only as small organized remnants or fibrous bands. Although spontaneously formed thromboemboli may not behave exactly like artificially produced clots, a similar although slightly more prolonged course of resolution has been described in man.[12] On the other hand, emboli which are aged in vivo for 2 to 3 weeks before their release into the circulation are invariably found on pathologic examination.[14] The reduction in size is slower initially and less fragmentation is found, but thereafter the processes of organization and resolution are similar to those with fresh emboli. Freiman states: "The slower rate of thrombolysis of these aged emboli appears attributable to the composition of the embolus at the time of its release and supports the view that their fibrin content may be less susceptible than freshly formed fibrin to endogenous fibrinolytic activity. Under these circumstances a larger portion of thrombotic material persists long enough to undergo organization."[14] Therefore, the rate of restoration of blood flow through an occluded pulmonary artery may be related to the age and fibrin content of the thrombus. Fresh emboli are apparently resolved with greater rapidity by endogenous fibrinolytic activity than are those retained longer in the veins prior to their release into the circulation.

Resolution of pulmonary embolism in man. Results of serial lung scans in the 20 patients studied indicate that the restoration of blood flow to lobar arteries after embolism occurs quickly and in some instances

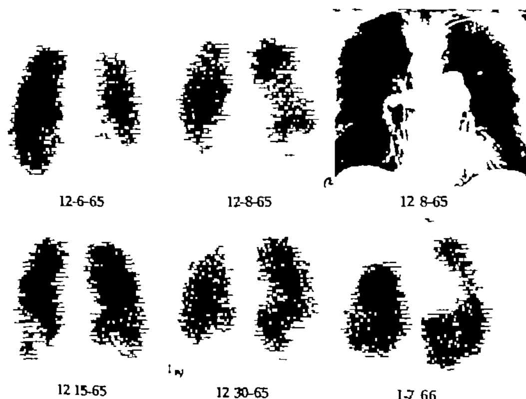


Fig 4 Case No. 5 (M.G.). Multiple segmental and subsegmental emboli. Rapid resolution of older lesions occurs while new ones develop. The sites of the occlusions are not demonstrable by angiography

in less than 1 week. Usually normal flow is re-established between 1 and 3 weeks. Although the available data are limited the findings indicate that large emboli are probably not resolved by the process of organization which takes 1 to 4 months[19] but, more likely by fragmentation, lysis, or contraction or by a combination of all three mechanisms. Experimentally the latter mechanisms account for the rapid resolution of large fresh emboli. In man it is also likely that large emboli come from recently formed thrombi. They are larger and more fragile than older thrombi which have become contracted and firm before their release into the circulation. In this study the absence of fatal embolization and the infrequent occurrence of any further embolization after adequate anticoagulation was obtained lends further support to this theory

In several patients with rapidly resolving lesions, the interval between the scans was too long to determine the recovery rates accurately However one patient (Fig 1) was scanned every 2 to 3 days during the early recovery phase. Perfusion to the right upper lobe increased progressively to normal over a period of 9 days The onset of recovery in the right lower and middle lobes was delayed about 1 week and then proceeded gradually during the succeeding 2 weeks. Although the data are too few to draw firm conclusions this well studied case supports a process of lysis rather than one of organization.

The 4-year-old boy with the septic embolus also had a lobar lesion but unlike the others, it did not resolve during 16 months of observation. Presumably an inflammatory reaction from the infected embolus led to thrombosis and possible fibrotic obliteration of the lumen of the vessel.

The wide range of rates of resolution with sublobar emboli likewise is not well understood However as in lobar embo-

Table I. Characteristics of patients and scan findings

Case	Initial	Age, sex	Predisposing condition	Classification of emboli	Recovery time	Scans performed	Duration of follow-up
1	R.B.	42 M	Thrombophlebitis	Lobar (RUL) b. Segmental (LLL) Segmental (LLL)	5 days 5 days No change 14 mo.	4	14 mo.
2.	T.B.	27 M	Thrombophlebitis	a. Segmental (LUL)	No change 1 mo.	3	1 mo.
3	B.C.	69 F	Congestive heart failure	a. Lobar (RUL) b. Segmental (bases)	6 days Slight improvement 6 days	3	9 day
4	R.E.	62 M	Varicose veins	a. Lobar (LLL) b. Lobar (LUL)	4 days No change 17 days	4	17 day
5.	M.G.	50 F	Thrombophlebitis	a. Segmental (LUL, LLL) b. Multiple segmental and subsegmental	No change 2 mo. 3-7 days	8	4 mo.
6.	C.H.	53 F	Thrombophlebitis	a. Segmental (RLL) b. Segmental (RUL)	1 mo. 3 mo.	5	3 mo.
7	C.K.	74 M	Unknown	a. Segmental (RLL) b. Segmental (RUL, LUL)	5 wk. Incomplete 4 mo.	3	4 mo.
8.	L.L.	58 F	Unknown	a. Lobar (RUL) b. Lobar (RLL, RML) Segmental (LLL) d. Subsegmental (LUL)	9 day 11 day 9 days 3-7 days	7	1 mo.
9	A.M.	52 F	Congestive heart failure	a. Multiple segmental and subsegmental	15 days to 2 mo.	6	14 mo.
10	I.M.	20 F	Thrombophlebitis	a. Multiple segmental	3-4 wk.	5	10 wk.
11	M.M.	62, F	Congestive heart failure	a. Multiple subsegmental	14 day	3	1 y
12.	P.M.	24 F	Pelvic thrombophlebitis	a. Segmental (LLL) b. Segmental (RLL)	10 days No change 4 mo.	5	4 mo.
13	J.N.	4 M	Bacterial endocarditis on a VSD	a. Lobar (RLL, RML)	No change 16 mo.	4	16 mo.
14	P.O.	69 M	Thrombophlebitis	a. Segmental (RUL)	No change 15 days	3	15 day
15.	R.P.	37 M	Thrombophlebitis	a. Lobar (RUL) b. Segmental (RLL)	7 day 11 days	3	11 day
16.	C.R.	81 M	Congestive heart failure	a. Segmental (RUL) b. Segmental (RLL) c. Multiple subsegmental	6-10 days 10-21 day Some by 21 day	4	21 day
17	C.R.	68 M	Thrombophlebitis	Segmental (RUL, RLL, LUL) b. Segmental (LLL)	Some by 11 day No change 6 wk.	5	6 wk.
18.	L.S.	58 F	Bed rest with fractured knee	a. Lobar (RLL) b. Lobar (RUL)	4-15 day 12 days	3	15 day
19	M.V.	59 F	Varicose veins	a. Lobar (RUL)	6 wk.	3	10 wk.
20.	W.V.	62, F	Thrombophlebitis with fractured hip	a. Lobar (RUL) b. Segmental and subsegmental (bases)	4 wk. 6 wk.	3	10 wk.

RUL, Right upper lobe. *RLL*, Right lower lobe. *LUL*, Left upper lobe. *LLL*, Left lower lobe. *VSD*, Ventricular septal defect.

lism the rapidly clearing lesions may have been caused by emboli from newly formed thrombi whereas the more persistent ones may have arisen from older thrombi. It is quite possible that many fresh segmental and subsegmental emboli resolved so rapidly that only the more mature emboli were detected.

Two important sources of error are inherent in this study. First, the shorter recovery times were underestimated in some cases because the onset of symptoms

did not necessarily coincide with the embolic event, and some emboli may have occurred asymptomatically with resolution already underway before the initial scan. Second the longer recovery times were sometimes overestimated because in these patients the scans were often repeated a week or more apart and recovery may have taken place well before the repeat scan was performed

Further scanning studies are underway to augment the available information on recovery rates from large and small pulmonary emboli Patients with lobar lesions will be scanned at shorter intervals and those with smaller emboli will be followed more closely In addition attempts will be made to determine the incidence and types of embolic lesions which may occur in patients with well known predisposing disorders. Such a study could lead to the prevention of those fatal attacks which are often preceded by small signal embolic episodes.

Summary and conclusions

Lung perfusion scans were performed three or more times in 20 patients with uncomplicated pulmonary embolism in order to determine their response to anticoagulant therapy and to estimate the rates of restoration of blood flow in lobar and smaller lesions Normal blood flow is usually (6 of 8 cases) re-established in lobar lesions within 1 to 3 weeks but recovery times are generally longer and much more variable with smaller lesions ranging from 4 days to 4 months. Further embolic episodes seldom occur during adequate anticoagulant treatment

Recovery rates from uncomplicated major and minor pulmonary embolism in man appear to be similar to those found experimentally Freshly formed clots in animals were resolved more rapidly than clots which were aged in vivo before their release into the circulation The difference in recovery rates found in this clinical study seems to be largely attributable to the age and fibrin content of the emboli

With further investigation of patients with pulmonary embolism and of others with known predisposing disorders, lung scanning can improve the diagnosis and management of this common disorder and conceivably those fatal attacks which are preceded by minor nonfatal embolic episodes can be prevented

We wish to express our appreciation to Judy Hurwit, Charles Balls, Madge Griffin, Jane Thompson and Mike Grant for technical assistance to Frances Vickles for preparation of the illustrations and manuscript to Hector Pimentel for photographic assistance to Dr Paul Numerof and Dr Gordon Lindenblad of E. R. Squibb & Sons, for donating radioisotopes used in this study and to the James Picker Foundation for institutional grant-in-aid to the Memorial Hospital of Long Beach.

REFERENCES

1. Sautter R. D Fletcher F W Emanuel, D A., Lawton, B R. and Olsen T G Complete resolution of massive pulmonary thromboembolism, J A.M A. 189:948 1964
2. Fred, H L. Axelrad, M. A., Lewis J M and Alexander J K. Rapid resolution of pulmonary thromboemboli in man, Cardiovas. Res. Cent. Bull. 3 111 1965.
3. Taplin, G. V Dore, E. K., and Johnson, D E. Suspensions of radioalbumin aggregates for photoscanning the liver spleen, lung and other organs, J Nucl. Med. 5:259 1964
4. Wagner H. N J Sabiston, D C., McAfee, J G Tow D E., and Stern, H S Diagnosis of massive pulmonary embolism in man by radioisotope scanning, New England J Med. 271:377 1964
5. Quinn, J L. Whitley J E., Hudspeth A J and Pritchard, R W Early clinical applications of lung scintiscanning, Radiology 82:315 1964.
6. Haynie, T P Hendrick, C. K and Schreiber M. H Diagnosis of pulmonary embolism and infarction by photoscanning, J Nucl. Med. 6:613 1965
7. Taplin, G. V Johnson, D E Kennady J C Dore, E. K Poe, N D Swanson, L V and Greenberg, A. Aggregated albumin labeled with various radioisotopes, Andrews, Kniseley and Wagner editors Radioactive pharmaceuticals, USAEC Div of Technical Information, pp 525-551 (1966)
8. Coon, W W and Willis, P W Deep venous thrombosis and pulmonary embolism prediction, prevention and treatment Am J Cardiol. 4:611 1959
9. Freiman, D G Suyemoto, J and Wessler S Frequency of pulmonary thromboembolism in man, New England J Med 272 1278, 1965
10. Marshall, R Pulmonary embolism Springfield, Ill 1965 Charles C Thomas, pp 61-66.
11. Wessler S Freiman, D G Ballon, J D Katz, J H Wolff R and Wolff E Experimental pulmonary embolism with serum-induced thrombi, Am. J Path 38:89 1961
12. Orell, S R The fate and late effects of nonfatal pulmonary emboli Acta Med Scandina 172:473 1962
13. Freiman, D G Wessler S and Lertzman, M Experimental pulmonary embolism with serum-induced thrombi aged in vivo, Am. J Path. 39:95, 1961

The effect of digitalis in compensated and decompensated patients with internal cardiac pacemakers

Ephraim Donoso, M.D.
William G. Stein, M.D.
*Lawrence J. Cohn, M.D.***
*Leonard Schloff, M.D.***
Charles K. Friedberg, M.D.
New York, N. Y.

Although the implantation of a cardiac pacemaker usually improves cardiac function in patients with complete heart block,[1-3] some patients remain in congestive heart failure in spite of adequate pacing, whereas other patients develop congestive heart failure some time after implantation of a pacemaker. We have studied the effect of digitalis in patients with fixed rate internal pacemakers with and without congestive heart failure. Digitalis has been reported to increase the cardiac output at rest in some patients with fixed rate pacemakers, but a correlation of digitalis effect with the clinical status and the effect of digitalis on exercise hemodynamics in such patients has not been previously reported.

Materials and methods

Nine patients in whom nonsynchronous internal cardiac pacemakers were implanted for the treatment of complete heart block were studied at rest and during exercise before and after digitalization. All were in complete heart block at the time of study, with complete ventricular capture by the pacemaker at rates of 65 to 71 per minute. They were divided into two groups according to the presence or absence of clinical congestive heart failure (CHF) at the time of study. Group I consisted of 3 patients in CHF and Group II consisted of 6 patients not in CHF. All of the patients of Group I and 5 of the patients of Group II had been in CHF prior to the insertion of a pacemaker. All of the patients were 65 years of age or older, but only 3 had evidence of atherosclerotic heart disease as indicated by a documented myocardial infarction in the past or a history of angina pectoris. Pertinent clinical data are summarized in Table I.

All patients were studied in the basal postabsorptive state without premedication. Studies were carried out with the patient in the supine position. A constant

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
Supported in part by Grant Nos. HE-07416-02, HE-22,186-01, HE-22,409-01, and FR-0 5300-04 from the United States Public Health Service.
Received for publication June 20, 1968.
Address: Cardiology Division, The Mount Sinai Hospital, 100th St. and Fifth Ave., New York, N. Y. 10029.
**United States Public Health Service Postdoctoral Fellow.

Table I. Clinical background of patients

Subject	Sex age	Pacemaker indication	Enlarged heart	Congestive heart failure	
				Before pacemaker	After pacemaker
Group I					
M H.	M 88	A S	+	+	+
V V	F 74	A S, CHF	+	+	+
J.Z.	M 73	A S CHF	+	+	+
Group II					
P I	M 74	CHF	+	+	−
D R.	M 83	A S	+	+	−
I M	F 78	A S	+	+	−
G.L.	M 81	A S	+	+	−
R.G	F 74	A S, CHF	+	+	−
R B	F 65	A S	+	−	−

A S Adams-Stokes syndrome; *CHF* Congestive heart failure.

level of exercise was performed at a fixed rate and workload on a bicycle ergometer This level was determined during a 10-minute period of practice exercise performed immediately prior to the actual study and was set as close as possible to the patient's maximum exercise tolerance during this period of practice exercise. All patients were able to repeat this level of exercise during the subsequent exercise periods of the study Oxygen consumption was measured in 3 patients by spirometry The remainder of the patients could not tolerate the mouthpiece Brachial arterial and venous pressures were measured with unbonded strain gauges. Mean pressures were determined electronically Cardiac outputs were measured in duplicate by the injection of indocyanine green into a catheter inserted into the antecubital vein A constant withdrawal pump was used to withdraw blood from the brachial artery through a cuvette densitometer All cardiac outputs were calculated by logarithmic extrapolation of the dye curves. All data were recorded on a photographic recorder

Subjects were studied first in the basal state and again during the fifth to ninth minutes of exercise Cardiac outputs were determined at 5 and 7 minutes of exercise and the exercise was continued until the second dye curve was completed Ouabain (0 01 mg per kilogram) was then infused intravenously over a 10-minute period Thirty minutes after the completion of the infusion of ouabain the subject was restudied in both the resting and exercise states.

In assessment of the changes in cardiac output that were seen the error of the dye-dilution method ±10 per cent, was used as the criterion of significance. Because of the small numbers of patients involved in this study statistical analysis was not practicable.

Results

Cardiac index (Table II) The resting cardiac index before ouabain in all 3 subjects in Group I (CHF) was 2 L min M or less (range 1 1 to 2 L min M) and 2 of the 3 manifested an increase with exercise After ouabain the resting cardiac index rose in of the 3 subjects and the exercise cardiac index increased in all 3

In Group II (no CHF) the resting cardiac index before ouabain was L min M or more in all 6 subjects (range 2 to 3 3 L min M) but in 3 subjects it was less than 7 L min M In 3 of the 6 the cardiac index increased with exercise whereas 3 subjects had a fixed cardiac index After ouabain the

Table II *Cardiac index before and after ouabain*

	Before ouabain			After ouabain		
	Resting atrial rate	Cardiac index (L./min./M²)		Resting atrial rate	Cardiac index (L./min./M²)	
		Resting	Exercise		Resting	Exercise
Group I						
M H	84	1 1	1 1	75	1 6	2 2
\ \	67	2 2	2 6	66	2 8	3 0
J Z	56	1 9	2 6	42	1 8	3 8
Average		1 7	2 1		2 1	3 0
Group II						
P I	80	2 3	3 2	63	2 3	3 6
D R.	76	2 2	3 8	72	2 1	3 4
R G	AF	2 9	2 9	AF	3 3	2 9
G L.	74	2 7	3 4	66	2 8	3 6
I M	AF	2 4	2 1	AF	2 2	2 0
R.B	68	3 3	3 2	67	2 3	3 3
Average		2 6	3 1		2 5	3 1

Differences in exercise cardiac indices accounted for by different oxygen consumptions
AF Atrial fibrillation

resting cardiac index was unchanged in 4 subjects increased slightly in 1 and fell markedly in 1 Five of the 6 had essentially the same exercise cardiac index as before ouabain whereas 1 subject had a slight fall in cardiac index.

Pressures The resting venous pressure was measured in 8 of the subjects and was normal in all except M H whose basal venous pressure was 16 mm Hg After ouabain most subjects showed a slight fall in venous pressure.

Although most patients attained a steady state after 5 minutes of exercise 3 patients (M H J Z C L) had a higher cardiac index after 7 minutes of exercise than after 5 minutes of exercise even though the amount of exercise being performed was held constant In these 3 subjects the increment was present both before and after the administration of ouabain Since the increment between 5 and 7 minutes was approximately the same both before and after digitalis the average of the 5- and 7 minute values was used in these cases. None of the patients had a 7 minute exercise value that was significantly (±10 per cent)[7] lower than the 5-minute value.

Discussion

The normal heart responds to exercise with increases in both the force of contractility (as measured by the first derivative of the pressure pulse)[8] and the cardiac output.[9,10] Systemic arterial pressures increase because of increased flow[4,1] and possibly changes in peripheral vascular impedance The increase in cardiac output with mild to moderate exercise is due primarily to an increase in the heart rate although with moderate to severe exercise stroke volume increases as well [1] However because of their fixed ventricular rate patients with implanted pacemakers can increase their cardiac output only by increasing their stroke volume

In patients with symptomatic heart disease the resting cardiac index is commonly below normal (less than 2 7 L./min./M²) [12-15] With exercise the cardiac index is either fixed or shows a moderate increase.[15-17] After the administration of digitalis glycosides, the cardiac index is increased both at rest and during exercise in patients in either overt or latent congestive heart failure whereas in patients without congestive heart failure there is no change in the cardiac index.[1,3,18]

Myocardial contractility usually increases irrespective of any change in cardiac output.[30,31]

Several workers have studied the response to exercise of patients with complete heart block who have artificial pacemakers. Bevegard[32] Hudson[2] and Sowton[33] found that in all of their subjects the cardiac indices were increased with exercise. However the resting cardiac indices in their subjects were considerably higher than those in our subjects, and therefore do not represent a suitable comparison. Benchimol and associates[1] reported an increased cardiac index with exercise in 6 of the 8 subjects whom they studied and the resting cardiac indices were comparable to those seen in our subjects.

Benchimol and associates[1] studied the effect of ouabain on the resting hemodynamics in 6 patients with complete heart block who had implanted pacemakers. The basal cardiac indices were similar to those seen in our patients. Four of their patients manifested an increased cardiac index after ouabain and the first derivative of the brachial arterial pressure pulse increased in 3 patients in whom it was measured.

The current study confirms these observations on the effect of digitalis and extends them to the exercise state. We have also demonstrated different effects in patients with and without congestive heart failure who have fixed rate cardiac pacemakers.

As in patients without pacemakers, two groups may be distinguished on the basis of the effect of ouabain on the cardiac output: those who respond to ouabain with an increased cardiac output (Group I) and those whose cardiac output does not increase after ouabain (Group II). In these patients the clinical evaluation of congestive heart failure was accurate in determining which patients would benefit from ouabain.

In some of our patients with sinus rhythm the atrial rate during some of the studies was nearly the same as the ventricular rate (Table II). An analysis of the simultaneously recorded electrocardiograms did not reveal any instance in which consistent synchronization of the atria and ventricles in the physiologic range (0.01 to 0.30 second) occurred.[34] Therefore it appears that the changes in cardiac output that were observed were due entirely to the pharmacologic action of digitalis.

Some of the patients in Group II had a resting cardiac index below the usually stated lower limit of normal (2.7 L./min./M.) and or failed to increase their cardiac index with exercise before digitalis. Both of these findings are abnormal and suggest cardiac dysfunction in these patients, but there was no clinical evidence of congestive heart failure. The low cardiac indices in our elderly patients may be a result of the aging process since both Brandfonbrenner and associates[35] and Granath and associates[36] have reported decreases in the cardiac index with age although not always below 2.7 L./min./M. and the response to exercise was impaired only slightly in the patients studied by Granath and associates.

Summary

Nine elderly patients (average age of 77 years) with complete heart block who had internal fixed rate cardiac pacemakers were studied in order to determine their response to ouabain in the resting and exercise states. Three patients were in clinical congestive heart failure and all 3 manifested significant increases in resting and exercise cardiac indices after ouabain. None of the 6 patients who were not in clinical congestive heart failure had a significant increase in cardiac index after ouabain and the exercise cardiac index was essentially the same before and after ouabain. In these elderly patients with complete heart block and fixed-rate internal pacemakers, digitalis appears to have improved cardiac function only in the presence of clinical congestive heart failure.

The pacemakers were inserted by Dr. Robert S. Litwak and Dr. Howard L. Gadboys. Dr. Sidney Fenig and Dr. Herbert Cohen assisted in this study.

REFERENCES

1. Benchimol, A., Li, Y. B., and Dimond, E. G.: Cardiovascular dynamics in complete heart block at various heart rates, Circulation 30:542, 1964.
2. Hudson, W. A.: Hemodynamic effect of artificial cardiac pacemaking in patients with complete heart block, Thorax 17:180, 1962.

3. Premme, T. E., Zitnik, R. S., Reed, D. P., Haynes, F. W., and Dexter, L.: Circulatory dynamics of artificial pacing in complete heart block in man, Circulation 28:784, 1963.
4. Benchimol, A., Palmero, H. A., Liggett, M. D., and Dimond, E. G.: Influence of digitalization on the contribution of atrial systole to the cardiac dynamics at a fixed ventricular rate, Circulation 32:84, 1965.
5. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies of the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiologic and pathologic conditions, Am. J. Physiol. 99:534, 1932.
6. Ahmed, S., Bayliss, R. I. S., Briscoe, W. A., and McMichael, J.: The action of ouabain (g-strophanthin) on the circulation in man, and a comparison with digoxin, Clin. Sc. 9:1, 1950.
7. Sleeper, J. C., Thompson, H. K., Jr., McIntosh, H. D., and Elston, R. C.: Reproducibility of results obtained with indicator-dilution techniques for estimating cardiac output in man, Circulation Res. 11:712, 1962.
8. Gleason, W. L., and Braunwald, E.: Studies on the first derivative of the ventricular pressure pulse in man, J. Clin. Invest. 41:80, 1962.
9. Holmgren, A., Jonsson, B., and Sjostrand, T.: Circulatory data in normal subjects at rest and during exercise in recumbent position with special reference to the stroke volume at different work intensities, Acta Physiol. Scandinav. 49:343, 1960.
10. Williams, M. H., Jr., Zohman, L. R., and Ratner, A. C.: Hemodynamic effects of cardiac glycosides on normal human subjects during rest and exercise, J. Appl. Physiol. 13:417, 1958.
11. Rushmer, R. F.: Constancy of stroke volume in ventricular responses to exertion, Am. J. Physiol. 196:745, 1959.
12. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr., and Cournand, A.: Some effects of digoxin upon the heart and circulation in man, Am. J. Med. 7:439, 1949.
13. Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., Ellis, L. B., and Lavin, M. R.: The effects of the cardiac glycosides upon the dynamics of the circulation in congestive heart failure. I. Ouabain, J. Clin. Invest. 27:588, 1948.
14. Ferrer, M. I., Conroy, R. J., and Harvey, R. M.: Some effects of digoxin on the heart and circulation in man. Digoxin in combined (left and right) ventricular failure, Circulation 21:372, 1960.
15. Selzer, A., and Malmborg, R. O.: Hemodynamic effects of digoxin in latent cardiac failure, Circulation 25:695, 1962.
16. Harvey, R. M., Smith, W. M., Parker, J. O., and Ferrer, M. I.: The response of the abnormal heart to exercise, Circulation 26:341, 1962.
17. Selzer, A., and McCaughey, D. J.: Hemodynamic patterns in chronic cardiac failure, Am. J. Med. 28:337, 1960.
18. Selzer, A., Hultgren, H. N., Ebnother, C. L., Bradley, H. W., and Stone, A. O.: Effect of digoxin on the circulation in normal man, Brit. Heart J. 21:335, 1959.
19. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., and Alexander, J. K.: Some effects of digoxin on the heart and circulation in man. Digoxin in enlarged hearts not in clinical congestive failure, Circulation 4:366, 1951.
20. Braunwald, E., Bloodwell, R. D., Goldberg, L. I., and Morrow, A. G.: Studies on digitalis. IV. Observations in man on the effects of digitalis preparation on the contractility of the non-failing heart and on total vascular resistance, J. Clin. Invest. 40:52, 1961.
21. Mason, D. T., and Braunwald, E.: Studies on digitalis. IX. Effects of ouabain on the nonfailing human heart, J. Clin. Invest. 42:1105, 1963.
22. Bevegard, S.: Observations on the effect of varying ventricular rate on the circulation at rest and during exercise in two patients with an artificial pacemaker, Acta Med. Scandinav. 172:615, 1962.
23. Sowton, E.: Hemodynamic studies in patients with artificial pacemakers, Brit. Heart J. 26:737, 1964.
24. Samet, P., Bernstein, W. H., Nathan, D. A., and Lopez, A.: Atrial contribution to cardiac output in complete heart block, Am. J. Cardiol. 16:1, 1965.
25. Brandfonbrener, M., Landowne, M., and Shock, N. W.: Changes in cardiac output with age, Circulation 12:557, 1955.
26. Granath, A., Jonsson, B., and Strandell, T.: Studies on the central circulation at rest and during exercise in the supine and sitting body position in old men. Preliminary report, Acta Med. Scandinav. 169:125, 1961.

Ventricular arrhythmias after precordial electric shock

Ephraim Donoso, M.D.
*Lawrence J. Cohn, M.D.***
Charles K. Friedberg, M.D.
New York, N. Y.

Although precordial electric shock is a widely used and relatively safe procedure for the conversion of cardiac arrhythmias,[1-4] new postshock arrhythmias are frequently seen.[1-4] These include serious ventricular arrhythmias[4] which may have been responsible for the death of some patients.[11] Digitalis has been implicated by some investigators as the etiological factor in these arrhythmias.[4,11] This poses a problem since many patients who require conversion have already required large doses of digitalis by the time that conversion is undertaken. We have therefore reviewed our experience with precordial electric shock in order to determine whether the postshock arrhythmias that we have seen are related to digitalis therapy, and to what extent the procedure itself was the cause of these arrhythmias.

Materials and methods

Synchronized D.C. shock was employed 58 times in 53 patients. Diagnoses and rhythms before shock are listed in Tables I and II. As can be seen, most of the patients were treated for atrial fibrillation and the most common etiologies were rheumatic and arteriosclerotic heart diseases. Twenty-six of the procedures were carried out while the patient was receiving only digitalis, 24 with the patient on both digitalis and either quinidine (22 patients) or procaine amide (2 patients), 3 with the patient on quinidine alone, and 5 patients had not received any cardiac medication. All patients were anesthetized with intravenous barbiturates. A Lown D.C. Cardioverter† set for zero delay was used. The first 53 procedures were performed with 3½-inch paddles positioned either anteriorly and laterally or anteriorly and posteriorly, and in the last 5 procedures 5-inch paddles positioned anteriorly and posteriorly were used.

Most patients received an initial shock of 50 or 100 watt-seconds. If this failed to restore sinus rhythm, successively larger shocks were given to a maximum of 400 watt-seconds.

A new arrhythmia was considered to have appeared if it was not present prior to the procedure. An increase in the frequency of ventricular premature systoles

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
Supported in part by Grant Nos. 2T1 HE 5240-06, FR-O 5800-04, and HE-22,899-01 from the United States Public Health Service.
Received for publication June 29, 1964.
Address: Cardiology Division, The Mount Sinai Hospital, 100th St. and Fifth Ave., New York, N. Y. 10029.
**United States Public Health Service Postdoctoral Fellow.
†Manufactured by American Optical Co., Chelsea, Mass.

Table I Diagnoses

Rheumatic heart disease	25
Arteriosclerotic heart disease	18
No heart disease	7
Miscellaneous	
Congenital heart disease	3
Sarcoid	1
Old myocarditis	1
Old pericarditis	1
Cardiomyopathy	1

There were 2 patients with two diagnoses, and 1 with three diagnoses

Table II Preshock cardiac rhythms

Atrial fibrillation	34
Atrial flutter	19
Paroxysmal supraventricular tachycardia with ventricular tachycardia	2
Ventricular tachycardia	1
Paroxysmal supraventricular tachycardia	2

that had been present before shock was not considered to be a new arrhythmia. In 3 procedures records suitable for complete analysis were not available for technical reasons.

Results (Table III)

Three patients scheduled for conversion experienced reversion to sinus rhythm after quinidine therapy had been started prior to shock and are not included in the present series

Sinus rhythm was restored 52 times in 58 procedures (90 per cent) but was maintained for more than 10 minutes only 47 times (81 per cent)

Atrial premature systoles were seen 29 times (53 per cent) sinus bradycardia (23 to 38 per minute) 4 times and periods of complete asystole twice. Paroxysmal supraventricular tachycardia developed in 5 cases (9 per cent) including 3 cases with irregular P P intervals and varying A V block. Nodal rhythm occurred in 9 cases (16 per cent) and A V dissociation was seen in 8 cases (15 per cent) Both slow (33 to 67 per minute) and fast (78 to 116 per minute) nodal rhythms were observed

Ventricular premature systoles were recorded in 26 procedures (47 per cent) They were unifocal in 11 and multifocal in 15 Their frequency was five or less per minute in 11 cases, and six or more per minute in 15 cases. Eleven cases occurred in patients receiving only digitalis, 12 cases in patients receiving both digitalis and either quinidine or procaine amide 2 cases in patients receiving only quinidine and 1 case in a patient who was not receiving any cardiac drugs. Ventricular bigeminy was seen in 17 of these procedures (31 per cent) 6 times in patients on digitalis alone 9 times in patients on both digitalis and quinidine once in a patient receiving only quinidine and once in a patient who was not receiving any cardiac medication Both unifocal and multifocal premature systoles, as well as bigeminal rhythm were seen in patients not receiving digitalis.

Ventricular fibrillation occurred in 2 patients. In neither was it due to improper synchronization since it occurred some time after the shock in both

One patient was a 56-year-old woman with rheumatic mitral stenosis enlarged heart congestive heart failure and atrial fibrillation with multifocal ventricular premature systoles who was maintained on digoxin 0 5 mg per day Twenty-five seconds after the third shock (400 watt seconds) a ventricular premature systole initiated ventricular fibrillation which later reverted to a coronary sinus rhythm with ventricular premature systoles and bigeminy

The second patient was a 61 year-old man with rheumatic aortic stenosis and mitral insufficiency markedly enlarged heart severe congestive heart failure and atrial fibrillation with ventricular premature systoles. He was maintained on digoxin 0 75 mg per day and diuretic therapy Quinidine 1 2 Gm per day was started one day prior to shock Forty seconds after the second shock (250 watt seconds) a ventricular premature systole initiated ventricular fibrillation which was terminated by a shock of 400 watt seconds However 22 seconds later another ventricular premature systole initiated a second bout of ventricular fibrillation This was terminated by another shock of 400 watt seconds, with the ap-

Table III

Rhythm	*Cases*	*Medication*				*Total energy before appearance of arrhythmia (watt seconds)*				*Number of shocks before appearance of arrhythmia*			
		Digitalis	*Quinidine*	*Digitalis and quinidine or procaine amide*	*None*	*50-100*	*120-200*	*220-300*	*320+*	*1*	*2*	*3*	*4+*
Unifocal ventricular premature systoles	14	5	2	7	0	11	1	1	1	11	2	0	1
Multifocal ventricular premature systoles	15	4	0	10	1	6	6	2	1	8	4	2	1
Ventricular bigeminy	17	6	1	9	1	9	4	2	2	10	4	2	1
Paroxysmal supraventricular tachycardia	5	0	0	5	0	2	0	2	1	2	0	2	1
Nodal rhythm	9	4	2	3	0	4	4	1	0	6	3	0	0
A-V dissociation	8	2	0	5	0	3	2	2	0	3	2	2	0
Ventricular tachycardia	3	2	0	1	0	1	2	0	0	2	1	0	0
Ventricular fibrillation	2	1	0	1	0	0	0	1	1	0	1	0	1
Atrial premature systoles	29	14	0	12	3	16	5	5	3	19	3	5	2
Sinus bradycardia	4	3	0	1	0	2	2	0	0	2	1	1	0
S-A arrest	2	1	0	1	0	2	0	0	0	2	0	0	0

*Includes patients who developed multifocal ventricular premature systoles after additional shocks.

pearance of atrial fibrillation with multifocal ventricular premature systoles and bigeminy.

Runs of paroxysmal alternating ventricular tachycardia were seen in 2 patients both of whom had multifocal ventricular premature systoles before the appearance of the rapid ventricular rhythm. One patient was receiving both digitalis and quinidine whereas the other was receiving only digitalis. One patient receiving only digitalis had transient ventricular tachycardia.

Except for two episodes of ventricular fibrillation in one patient which were terminated by additional D.C. shock, all arrhythmias either diminished or disappeared spontaneously within an hour. However, nodal rhythm persisted in 2 patients, for 1 day in one and for days in the other. Arterial embolization was seen twice, both times in nonrheumatic patients without prior histories of embolization who had not received anticoagulants prior to the procedure. One instance of embolization occurred 4 days, and the other 8 days after successful conversion while both patients remained in sinus rhythm.

The P-R interval could be measured accurately in 46 of the cases in which sinus rhythm was restored. In 19 (44 per cent) the P-R interval was prolonged to more than 0.20 second. Eight of these patients were receiving only digitalis, 10 were receiving both digitalis and either quinidine or procaine amide, and 1 was not receiving any cardiac drugs. Nine of these 19 patients showed shortening of the prolonged P-R interval within 15 minutes. However, in 14 patients there was persistent prolongation of the P-R interval. Transient S-T elevation was seen in 2 patients.

Discussion

Both supraventricular and ventricular arrhythmias are commonly seen after

electric shock in the present series Most workers have emphasized the frequency of supraventricular arrhythmias and our experience is in accord with their findings[3-4,10 13 20] However except in the series of Reinikainen and associates[13] and that of Oram and Davies, the reported incidence of ventricular arrhythmias has been relatively low Some reports have noted that ventricular premature systoles are common after shock but the actual incidence is usually not given nor the number of patients who had this arrhythmia prior to shock[1,4 11 18] Ventricular premature systoles were seen after shock in 10 of 62 patients (16 per cent) in Killip's series and in 10 of 49 patients (24 per cent) in Castellanos series[12] but all of the patients with this arrhythmia also had it prior to the shock Isolated case reports of ventricular arrhythmias have appeared[7] but these do not give the over all incidence of these arrhythmias.

It is significant therefore, that new ventricular arrhythmias (tachycardia fibrillation premature systoles) were seen in 27 of 55 procedures (49 per cent) This incidence is higher than that reported by Reinikainen and associates[13] (27 per cent) and Oram and Davies[4] (33 per cent) The relationship of ventricular premature systoles to ventricular tachycardia and fibrillation is evidenced by the observation that ventricular premature systoles, usually *multifocal or bigeminal preceded* ventricular tachycardia and fibrillation in all 5 cases in this series. In the 2 fatal cases of ventricular fibrillation reported by Gilbert and Cuddy multifocal or bigeminal ventricular premature systoles were present prior to ventricular fibrillation

Digitalis therapy has been invoked as a cause of these arrhythmias by several investigators. Lown[3] and Killip[8] were the first to suggest this relationship because of the similarity of the postshock arrhythmias to those seen in digitalis intoxication. The only deaths that were apparently due to electric shock of which we are aware occurred in patients on digitalis. Both of the deaths reported by Rabbino and associates[10] occurred in patients who were in apparent digitalis intoxication and the fatal arrhythmias occurred immediately after the procedure However the 2 deaths cited by Gilbert and Cuddy[11] were seen in patients on moderate doses of digitalis, and the fatal arrhythmias occurred several hours after electric shock. Gilbert and Cuddy[11] also reported an absence of ventricular arrhythmias in 5 patients who either had been off digitalis for 5 to 10 days or had never received the drug However Reinikainen and associates[13] reported ventricular premature systoles in 7 of 25 patients (28 per cent) in whom digitalis was either withheld or never given as compared to an incidence of 10 of 28 patients (27 per cent) who received digitalis therapy without interruption. Of 11 patients who had never received digitalis, 4 (29 per cent) manifested ventricular premature systoles. This agrees with our finding of an incidence of ventricular premature systoles of 50 per cent (24 of 48) in the patients on digitalis and 43 per cent (3 of 7) in the patients not receiving digitalis. Although the number of cases is too small for a valid statistical analysis It is significant that new unifocal and multifocal ventricular premature systoles, as well as ventricular bigeminy were observed in patients not receiving digitalis (Table III) Since many patients were receiving diuretic therapy the depletion of potassium may have intensified the likelihood of arrhythmias in some patients, but we did not have sufficient data to *analyze this point.*

It is of note that both patients who developed ventricular fibrillation were receiving large doses of digitalis, and in both there was evidence suggestive of digitalis toxicity prior to shock On the other hand early in our experience with electric shock before the hazard of digitalis intoxication was appreciated a patient with digitalis-associated paroxysmal supraventricular tachycardia with block was successfully restored to sinus rhythm by electric shock after procaine amide and potassium therapies had proved to be unsuccessful.[7]

In an attempt to explore the possible effect of digitalis dosage we made an analysis of the dose of digoxin and the incidence of new ventricular arrhythmias in the 39 patients who were on a stable maintenance dose of digoxin There were

19 procedures on patients receiving 0.5 mg. of digoxin or more per day, and new ventricular arrhythmias were observed 9 times (47 per cent). In the 20 procedures in which the dose was less than 0.5 mg. of digoxin per day, the incidence was 10 (50 per cent). Therefore, except in the 2 patients with preceding ventricular irritability possibly due to digitalis overdosage, digitalis therapy did not appear to influence the incidence of ventricular arrhythmias. This conclusion is supported by recent experimental work of Lown and associates,[1] who found that digitalis was not a factor in postshock ventricular tachycardia unless toxic or nearly toxic doses of digitalis were used.

Since digitalis therapy did not adequately explain the arrhythmias that were seen, a further analysis was made of other factors in the procedure. The role of high levels of energy was suggested by the experimental data of Lown and associates in dogs in which postshock ventricular tachycardia was more common with higher levels of energy. Lown subsequently stated[3] that postshock arrhythmias in human beings are more common with high levels of energy, although specific data were not given. In the cases reported by Castellanos and associates[10] postshock ventricular tachycardia occurred only after shocks of 300 watt-seconds or more. In our cases, ventricular tachycardia was seen after shocks of 100, 120, and 200 watt-seconds, whereas ventricular fibrillation appeared after shocks of 250 and 400 watt-seconds.

When the total energy delivered and the number of shocks were analyzed, there was a correlation of both of these factors with the incidence of new ventricular arrhythmias (Table IV). Patients receiving only a single shock of 100 watt-seconds or less had a 40 to 42 per cent likelihood of such arrhythmias as compared to a 67 to 70 per cent risk for patients who received either more than three shocks or more than 400 watt-seconds. However, neither value was significant at the p = 0.05 level (p = 0.10 for both factors).

An alternate explanation for the higher incidence of new ventricular arrhythmias after multiple shocks and high levels of energy is that both are employed in patients with refractory arrhythmias that are more difficult to convert and therefore require multiple shocks and higher energies. Patients with refractory arrhythmias are probably those with more advanced forms of heart disease, and it may be the severity of the heart disease rather than the amount of shock employed that determines the likelihood of ventricular arrhythmias. However, since an accurate grading of the severity of the patients' heart disease was not practicable, this question cannot be answered.

The role of antiarrhythmic drugs was investigated by Castellanos and co-workers who found that quinidine reduced the incidence of supraventricular arrhythmias[12] but appeared to increase the incidence of ventricular arrhythmias.[11] However, the group with ventricular arrhythmias comprised only 4 patients, and 3 of the patients

Table IV. Total shock and energy

	Cases	Number of shocks				Total energy used (watt-seconds)				Medication			
		1	2	3	4+	100	200-300	300-400	500+	Digitalis	Quinidine	Digitalis and quinidine or procaine amide	None
Ventricular arrhythmias	27	11	5	4	7	10	5	2	10	11	2	13	1
No ventricular arrhythmias	28	17	5	3	3	14	6	3	5	13	0	11	4

had the same arrhythmia prior to shock. In the present series prior treatment with either quinidine or procaine amide did not appear to affect the incidence of new ventricular arrhythmias (Table IV)

Analysis of the 19 patients with first degree A V block after reversion to sinus rhythm revealed that only 1 patient was not receiving digitalis However the rapid improvement in A V conduction seen in 9 of these patients makes it unlikely that digitalis was responsible. It appears to be more likely that electric shock exerts a temporary depressant effect on A V conduction This is similar to the temporary depressant effect of electric shock on the S-A node described by Castellanos and associates.[12]

From the data presented it appears that, except for those patients on toxic doses, digitalis was not important in producing postshock arrhythmias and that these arrhythmias are more likely to be a consequence of both the amount of electric shock employed and the severity of the underlying heart disease.

Summary

New cardiac arrhythmias occurred 43 times in 50 patients who underwent 55 elective precordial applications of synchronized D C shock for the control of cardiac arrhythmias. Ventricular arrhythmias were seen after 27 procedures. There were *unifocal ventricular premature systoles* in 11 multifocal ventricular premature systoles in 15 and ventricular bigeminy in 17 Three of these patients developed runs of ventricular tachycardia and 2 developed ventricular fibrillation One patient with ventricular fibrillation received additional D C shock to control this arrhythmia. Except for this one patient all arrhythmias were transient and self limited All patients survived the procedure and there were no complications due to the new arrhythmias.

Although there were only 7 patients who were not receiving digitalis, 3 of these 7 patients developed new ventricular arrhythmias (bigeminy unifocal and multifocal premature systoles) This suggests that, in these patients electric shock acted to increase ventricular irritability even though there were no cases of ventricular fibrillation or tachycardia in this small group Furthermore in those patients who were not receiving toxic doses of digitalis, the dose of digitalis being used did not appear to be an important factor in determining which patients would develop new ventricular arrhythmias. Ventricular arrhythmias were more frequent after multiple shocks and high levels of energy This may have been due either to a dose-dependent pro-arrhythmic effect of electric shock or to the severity of the underlying heart disease that necessitated multiple shocks of high energy or to both

REFERENCES

1 Zoll, P M and Linenthal, A. J AC and DC countershock for arrhythmias, J.A M.A 188: 327 1964
2 Lown, B Cardioversion of arrhythmias, I and II Mod. Concepts Cardiovas Dis. 33:863 and 869 1964
3. Killip, T Synchronized DC precordial shock for arrhythmias, J.A.M.A. 186 1 1963
4 Oram S. and Davies, J P H. Further experience of electrical conversion of atrial fibrillation to sinus rhythm Lancet I 1294 1964
5. Zoll, P M and Linenthal, A. J Alternating current countershock for arrhythmias, Circulation 30:Suppl. III 180, 1964
6. Shaver J A. Kroetz, F W Tenicela, R Lancaster J F nd Leonard J J Post cardioversion ventricular tachycardia, Am. J Cardiol. 15 146 1965
7 Willis, W H Letter to the editor Am Heart J 67:575 1964.
8 Graf W S., nd Etkins, P Ventricular tachycardia after synchronized direct-current countershock, J.A.M.A. 190:470, 1964.
9 *Ross, E. M Cardioversion causing* ventricular fibrillation, Arch Int. Med. 114:811 1964
10. Rabbino, M D Likoff W and Dreifus, L. S.: Complication and limitations of direct-current countershock, J.A.M.A. 190:417 1964
11. Gilbert, R., and Cuddy R. P Digitalis intoxication following conversion to si us rhythm Circulation 32:58, 1965
12. Castellanos, A. Lemberg, L., Gosselin, A and Fonseca, E J Evaluation of countershock treatment of trial flutter Arch. I t Med. 115:426, 1965.
13. *Relolkalnen, M., Koskinen, P Pontinen, P* nd Siitonen, L.: Experiences in the use of direct current cou tershock in the treatment of cardiac arrhythmias, Acta Med. Scandina 178:Suppl. 437 1 1965
14 Morris, J J Kong, Y North W C and M I tosh H D Experience with cardioversion of trial fibrillation and flutter Am. J Cardiol. 14:94 1964
15 Brown, K. W G., Whitehead, E. H nd Morrow J P Treatment of cardiac arrhythmias with synchronized electrical countershock, Canad. M A J 90:103, 1964.

16. DeSanctis, R. Electrical conversion of ventricular tachycardia, J.A.M.A. 191:632, 1965.
17. Corwin, N. D., Klein, M. J., and Friedberg, C. K. Countershock conversion of digitalis-associated paroxysmal atrial tachycardia with block, Am. Heart J. 66:804, 1963.
18. Lown, B., Kleiger, R., and Williams, J. Cardioversion and digitalis drugs. Changed threshold to electric shock in digitalized animals, Circulation Res. 17:519, 1965.
19. Lown, B., Neuman, J., Amarasingham, R., and Berkovits, B. Comparison of alternating with direct current electroshock across the closed chest, Am. J. Cardiol. 10:223, 1962.
20. Castellanos, A., Fonseca, E. J., Gosselin, A., and Lemberg, L. Ventricular arrhythmias induced by direct-current countershock, Circulation 30(Suppl. III):59, 1964.
21. Castellanos, A., Gilmore, H., Lemberg, L., and Johnson, D. Countershock exposed quinidine syncope, Am. J. Cardiol. 15:127, 1965.
22. Lemberg, L., Castellanos, A., Swenson, J., and Gosselin, A. Arrhythmias related to cardioversion, Circulation 30:163, 1964.

Subadventitial fibroplasia of the renal artery, a disease of young women

Lawrence J McCormack M.D *
Thomas J Noto Jr M.D **
Thomas F Meaney M.D
Eugene F Poutasse M.D **
Harriet P Dustan M.D
Cleveland Ohio

Subadventitial fibroplasia is one of the common nonatherosclerotic stenosing lesions of the renal artery associated with hypertension In our earlier reports,[1-3] it was recognized as being different from other fibrosing diseases and was termed mural fibrosis. Although this lesion is commonly called fibromuscular hyperplasia,[1-4] it appears to be a distinct entity having characteristic microscopic and arteriographic features.

A recent survey of renal arterial disease[5] has shown subadventitial fibroplasia to be a disease primarily of the right renal artery and primarily of women between the ages of 20 and 40 years. This retrospective report describes the clinical radiographic and pathologic features of this disease in 31 hypertensive patients who were treated surgically either by revascularization operations or nephrectomy

Clinical material and methods of study

All patients had been referred to the Cleveland Clinic for the investigation of hypertension They were hospitalized for preoperative study which included measurements of brachial arterial blood pressure four times daily standard intravenous urography and renal arteriography either by translumbar aortic[6] or selective renal arterial injection of sodium diatrizoate.[6] Function tests of the individual kidneys were performed in 12 patients, using either water diuresis or mannitol diuresis with Pitressin details of this procedure and the analytic methods employed have been previously described[7]

Arterial segments obtained at the time of operation were fixed according to standard methods. Longitudinal and cross sections were stained with hematoxylin and eosin Mallory Heidenhain Masson trichrome, Verhoeff Van Gieson Gomori elastic and toluidine blue stains.

For the purposes of this study information concerning preoperative status was obtained from a review of the clinical records, intravenous urograms, and renal arteriograms. Measurements of the lengths of the kidneys were made on urographic

From the Division of Pathology the Division of Research, the Division of Radiology and the Department of Urology The Cleveland Clinic Foundation, Cleveland, Ohio.
This study was supported in part by Grant No. H-4435 from the National Heart Institute, Bethesda, Md and Grant No. HTS-5406 from the United States Public Health Service Washington, D C.
Received for publication June 27 1964.
*Address, Division of Pathology Cleveland Clinic, 2020 East 93rd St Cleveland, Ohio, 44106.
**Formerly Special Fellow in Cardiology Present Address: 1333 South Miami Ave Miami, Fla.
***Formerly member of the staff, Department of Urology The Cleveland Clinic Foundation. Present address 901 Medical Tower Norfolk, Va.

films in 23 of the 31 cases. In 8 these measurements were obtained from arteriograms because on two sets of urographic films the outlines of the kidneys were not clear and in 6, urography had been performed prior to referral of the patient here and was not part of our permanent record.

Study during return visits of the patients or correspondence with local physicians provided information concerning the long range antihypertensive effects of surgical treatment in 24 patients. The 3 patients who died after operation were, of course, excluded from this analysis so also were 3 patients who disappeared without trace and 1 who died from a combination of ileocolitis and chronic renal failure.

Results

Clinical features. Of the 31 patients 26 were females and 5 were males. Although the age range of the former was from 14 to 48 years, 21 were between the ages of 20 and 40 years—13 patients were in the third decade and 8 in the fourth. The 5 men were from 14 to 40 years of age (Table I).

Sixteen patients had known of hypertension for 1 year or less, but in most of these the blood pressure had not been measured frequently enough prior to that time to permit any conclusion concerning the real duration of hypertension. Seven patients had been hypertensive for more than 5 years; one of these, 27 years old, had had an elevated blood pressure at the time of the first measurement, 19 years previously. Generally speaking, hypertension was not severe and preoperative diastolic arterial pressure averaged less than 120 mm Hg in 21 patients. Only one patient (No. 14) had retinal hemorrhages and exudates and papilledema. Total renal excretory function was within normal limits in all patients, even in the 4 who had bilateral lesions and in the 4 who had single kidneys. Nine patients had bruits in the epigastrium or upper abdominal quadrants, and in 6 none was heard. The clinical records contained no mention of the presence or absence of bruits in 16 patients.

Intravenous urograms. Four patients had only one kidney, the other had been removed. In 3 patients nephrectomy had been performed because of pyelonephritis or renal lithiasis; the fourth patient, who had bilateral renal arterial disease, was first seen after a revascularization operation on the right side had failed and nephrectomy had been performed. These single kidneys were not atrophic; in fact, three actually seemed to be larger than normal, measuring 14 to 14.5 cm. The length of the kidney of the other patient was 12.0 cm, which was normal for her size.

In the 27 patients who had both kidneys marked differences in the lengths of the kidneys were found. There were 19 patients with unilateral arterial stenosis and in all the affected kidney was smaller than the unaffected one. Differences in length ranged from 1.0 to 4.8 cm and averaged 2.4 cm. Of the 8 patients with bilateral lesions, one had kidneys of equal size, but in 3 there was disparity between the lengths of the kidneys, ranging from 2.0 to 4.0 cm.

Renal arteriogram. Renal arteriography showed subadventitial fibroplasia to be a severely stenosing lesion (Fig. 1). The right renal artery was affected in 16 patients and the left, in 7 (Table I). Eight patients had bilateral disease, but in 6 of these the stenosis was much more severe on the right side. Usually, the lesion was found in the mid and distal portions of the main trunk and in only 3 patients was the proximal segment affected. Disease was often seen in the primary arterial branches; in 2 patients this was the only site, and the main renal arteries were unaffected; however, in 14, lesions occurred in the branches in association with stenosis of the main trunk.

The apparent length of the lesions, as judged by arteriograms, varied from a sharply localized segment to the distal two thirds of the main renal artery and primary branches. The types of arteriographic patterns seen are shown in Fig. 2. Characteristically, stenosis of the main trunk was variably severe (Figs. 1 and 2) and this produced a type of beading quite different from the aneurysmal beading seen in medial fibroplasia (Fig. 3 B). Disease of the branches was manifest either as stenosis or as a sausage-like dilatation (Fig. 2). Prominent collateral blood supply through capsular, perinephric and ureteral branches was found in 11 patients (Figs. 1, 3, 4, and 4). Because it was seen in all four selective arteriograms, we suspect that it is usually present, but that translumbar aortography, which was performed in 27

Table I Sex, age, site of lesions, operations performed, and results of operation in 31 patients with subadventitial fibroplasia

Patient			Lesion			Original operation			Second operation	Blood pressure (mm. Hg)		Months of observation
No.	Sex	Age	Side	Site (Right)†	Site (Left)	Type‡ (Right)	Type (Left)	Course§		Preop	Postop	
1	F	27	R	Mid		E		U		170/115	120/80	24
2.	F	38	R	Dist B		E		U		231/116	138/91	34
3	F	35	R L	Dist 2/3 B	Mid	E		U		167/114	140/90	34
4	F	38	R	Prox		E		U		150/103	120/80	48
5	F	30	R	Dist 2/3		E		U		177/113		1
6	F	19	R	Dist 2/3 B		E		U		140/100	110/70	25
7	F	48	L(sk)		Dist B		F	U		204/114		10 days
8.	F	40	R L	B	B		E	U		150/105	120/96	13
9	F	24	R L	Mid	Dist, B	E		U		216/123	157/98	96
10.	F	31	L		Mid	E		U		175/107	125/90	60
11	F	27	R L	Mid	Mid	E	E	U		172/112	112/72	8
12.	F	29	L		Mid		E	U		177/109	118/74	42
13	F	31	R	Dist 2/3		E		U		190/110	114/74	5
14.	F	25	R L	Mid	Mid	V	E	C	T	146/96		12
15.	F	43	R	Mid		E		C	N	177/110	180/112	48
16.	F	23	R	Dist 2/3, B		E		C	N	149/104	126/82	48
17	F	27	R	Dist		E		C	E	195/115	110/80	77
18.	F	21	R-L	Dist 2/3 B	Dist	E		C	VPG	202/127	120/93	74
19	F	28	R	Dist		E VG		C	V	188/120	135/83	33
20.	F	27	R	Dist 2/3		E,VG		po death		180/120		
21	M	33	R	Dist 2/3 B		E,VG		U		184/112	105/76	9
22.	M	19	L		Prox		AG	C	N	160/100	168/84	24
23.	F	27	R(sk)	Dist 2/3 B		AG		po death		203/133		
24.	F	21	R(sk)	Dist		AG		U		194/139	138/94	13
25.	F	27	L		Mid B		E, AG	U		174/104		1
26.	M	17	L(sk)		Dist, B		SRA	po death		204/140		
27	F	14	R L	Prox	Mid	SRA		C	N	154/110	110/70	65
28.	M	20	R	Dist 2/3 B		N		U		160/108	110/70	58
29	F	36	R	Dist 2/3		N		U		170/112	168/110	39
30.	F	32	R L	Dist 2/3 B	Dist	N		U		220/140	170/115	3
31	M	40	L		B		SN	U		238/138	205/130	68

*(sk) Single kidney.
†Prox, Mid, Dist: Proximal, mid, and distal segments of renal artery. Dist 2/3 = Mid and distal two-thirds segments. B = Primary arterial branch.
‡Type of operation: E = Excision of stenotic segment with end to end anastomosis. E,VG = Excision and insert vein graft. AG = Bypass arterial graft. SRA = Splenorenal anastomosis. N = Nephrectomy. SN = Segmental nephrectomy. T = Thrombectomy. VPG = Vein patch graft.
§Course refers to events occurring not only in the immediate postoperative period, but also during long term observation. U = Uncomplicated. C = Complicated. po death = Death attributed to the operation.

patients, did not give sufficient detail to show the collateral vessels.

Function tests. Function tests of individual kidneys were performed in 11 patients with unilateral lesions of the main renal artery and in one with bilateral lesions. When compared with results from the unaffected or less affected kidney, functions of the affected side were strikingly different. The flow of urine was decreased by a mean of 76 per cent (range 48-94 per



Fig. 1. Selective right renal arteriogram shows the notably severe stenosis in the distal portion of the renal artery, characteristic of subadventitial fibroplasia.

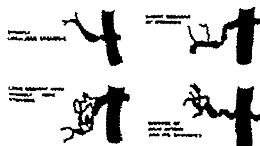


Fig. 2. Types of arteriographic patterns commonly found in subadventitial fibroplasia.



Fig. 3. Comparison. *A,* The arteriographic features of subadventitial fibroplasia (*A*) and medial fibroplasia (*B*). Both arteries could be said to be "beaded." However, in subadventitial fibroplasia (*A*) the "beads" are not wider than the unaffected proximal segment of the artery. In contrast, in medial fibroplasia (*B*) the "beads" represent aneurysms and the affected areas of the artery are wider than the unaffected portion.



Fig 4 A typical selective arteriogram of subadventitial fibroplasia show severe stenosis and rich collateral arterial supply through capsular blood vessels.

cent) The urinary concentration of sodium was reduced by an average of 70 per cent (range 39-96 per cent) and urinary osmolality increased by 29 per cent (range 0-50 per cent) With the exception of one patient who had equal values, the glomerular filtration rates of the affected kidneys were sharply decreased Excluding that patient, the average reduction for the group was 51 per cent (range 34-81 per cent) Generally speaking the decreases in the size of the kidneys, measured on the urographic films, paralleled the decrease in filtration rate as measured by clearances of mannitol and inulin

Pathologic features These features were remarkably uniform in appearance from patient to patient. The disease involved primarily the media and *elastica externa* occasionally a small portion of the adventitia seemed to be affected (Fig 5) The lesion consisted of a collar of dense collagen surrounding the main renal artery for distances varying from a few millimeters to 2 centimeters.

With cross-sectional studies the zone of collagen could be seen to replace the media to a variable extent, so that in some areas there was little left (Fig 5) Considerable disorganization was also seen with muscle



Fig 5 Photomicrograph of a renal artery shows collagenous thickening of the outer portion of the vessel with variable thinning of the media. The *elastica interna* is intact and the intima is normal. (Hematoxylin and eosin, X65.)



Fig. 6. Photomicrograph of renal artery with phosphotungstic acid hematoxylin stain showing separation of muscle bundles of the media by collagen. The dark areas near the top are remnants of the media, and the collagenous collar is below (×85).



Fig. 7. Photomicrograph. Small muscle bundles can be seen incorporated into the outer portion of the thick paramedial collagenous collar surrounding the renal artery. The more central portion of the media is somewhat disorganized and there is subintimal intimal fibroplasia. (Masson trichrome, ×80.)

bundles separated widely by collagen (Fig 6) Any of the special stains for collagen (Masson trichrome or Mallory Heidenhain) showed the abnormalities vividly but Mallory's phosphotungstic acid hematoxylin was particularly good for showing the amount of media replaced by the collagen (Fig 6) Elastic stains demonstrated that the dense portion of the *elastica externa* was partially to completely lost However circumferential strands of elastica that occur in the adventitia could always be recognized Involvement of part of the adventitia was suggested by the occasional incorporation of isolated bundles of smooth muscle into the outer part of the collagenous collar—these bundles represent the muscle clusters found in the adventitia of the renal artery (Fig. 7) However another possibility is that these bundles had originally been part of the media and had been displaced by the collagen The intima was occasionally thickened (Fig 7) but the thickening was usually slight and seemed to be an insignificant aspect of the lesion In only one instance was thrombosis found

Longitudinal sections contributed the additional finding that the fibrosis was of varying thickness, and it seems to be possible that this explains the variably severe stenosis found by arteriography

A single specimen of renal artery showed an alteration of the *elastica externa*, which may represent an early stage in the genesis of this lesion (Fig 8,A and B) This specimen was from the left renal artery of a patient with bilateral disease. Arteriography had shown a severely stenosing lesion on the right and minimal arterial disease on the left Both lesions were resected the one on the right side was characteristic of subadventitial fibroplasia The lesion on the left was quite different the media was intact but the dense portion of the *elastica externa* was the site of deposition of collagen which partly to completely replaced the elastica.

Surgical treatment Hypertension was treated surgically by nephrectomy or procedures designed to remove or bypass the occlusive disease (Table I) In 18 patients (Nos. 1 18) the disease was localized enough to permit excision and end-to-end arterial anastomosis. Nine of these patients had disease of the right renal artery and 3 of the left 6 had lesions on both sides. In only 2 of these 6 were bilateral operations performed (Nos. 11 and 14) and in the other 4 removal of the more severe stenosis restored arterial pressure to normal

Seven patients (Nos. 19-25) had such long stenotic segments that excision and primary arterial anastomosis were not possible so that some type of graft was required In 3 (Nos. 19 21) the diseased portion was excised and vein grafts were inserted Aorta renal artery bypass grafts were performed in another 3 (Nos. 22 24) and in one (No. 25) the lesion was resected and an inset hypogastric artery used Splenorenal anastomosis was carried out in 2 patients (Nos. 26 and 27) Three patients (Nos. 28-30) were treated by total nephrectomy and one (No. 31) by segmental nephrectomy

These treatments were marked by an unusual number of complications and by excellent therapeutic responses in those patients whose operations were technically successful. Complications occurred either in the immediate postoperative period or from 3 months to 3 years later (Details of these are presented in the accompanying *Appendix.*)

Hemorrhage and thrombosis occurred postoperatively A young woman (No. 20) died of hemorrhage when the proximal suture line of an ovarian vein graft disrupted Thrombosis developed in 6 patients and 2 patients with single kidneys (Nos. 23 and 26) died as a result thereof Another patient (No 14) with a single kidney underwent a thrombectomy after which renal excretory function was recovered slowly Nephrectomy was performed in the other 3 patients.

Stenosis recurred in 4 patients. In one patient (No 19) this probably was established within 3 months after excision of the lesion and insertion of an ovarian vein graft. By this time hypertension had returned but it was not until 6 months postoperatively that arteriography was performed and showed stenosis at the proximal suture line In the other 3 patients (Nos. 16 17 and 18) restenosis did not occur until about 3 years after operation. In each the operative procedure had

been excision of the affected arterial segment with end-to-end anastomosis. Two of these 4 patients (Nos. 16 and 19) were operated upon a second time with the plan of resecting the stenotic segment; the procedures were unsuccessful because of thrombosis, and nephrectomy was performed. In another patient (No. 17) a second resection was possible, but stenosis recurred. In the fourth patient (No. 18) a second operation was performed and hypertension again remitted.



Fig. [illegible] Photomicrographs of what seem to be early stages in the development of subadventitial fibroplasia beginning within the dense portion of the *elastica externa* (area of thickening (A), which stains as collagen. Note the partial loss of the *elastica* and, also, its displacement to the adventitia. At the left of the photomicrograph the staining characteristics and width of the *elastic externa* are normal. Photomicrograph *B* shows what seems to be a somewhat later stage. The *elastica externa* is more extensively displaced, and invasion of the media has begun. (Verhoeff-Van Gieson. ×83.)

Table II Response of arterial pressure to surgical treatment in 23 patients with subadventitial fibroplasia*

Operation	Number	Arterial pressure		
		Normal	Decreased	Unchanged
Excision	12	11	1	
Excision and vein graft	1	1		
Bypass graft	1		1	
Nephrectomy	9†	5		4
Totals	23	17	2	4
Per cent of total		74	9	17

*This number excludes the 3 patients who died postoperatively, the patient with colitis who died 1 year later, 3 patients who could not be traced, and 1 with restenosis who has not had a second operation.

†This number includes 4 patients for whom nephrectomy was the primary operation, and 5 in whom it was the second operation after failure of the first. In 2 of the 5 patients, the first operation had been excision, and in one each, excision and vein graft, bypass arterial graft, and splenorenal anastomosis.

The response of arterial pressure to surgical treatment could be judged in 23 of the 31 patients (Table II). This number excludes the 3 patients who died as a result of the operations, 1 patient with untreated restenosis, 3 patients whom we have been unable to trace, and 1 patient in whom thrombectomy was performed. The latter patient (No. 14) had had chronic ulcerative colitis for years, and her death 1 year after the renal arterial surgery seemed to be attributable to her chronic intestinal disease in addition to poor renal function.

Four of the 23 patients have been followed for less than a year after operation. They have been included in this analysis because our previous experience[4] had shown that the initial response of arterial pressure is a good indication of the long-term response if restenosis does not occur. The other 19 patients have been followed from 15 to 96 months.

In 17 (74 per cent) of the 23 patients, arterial pressure was normal; in 2 (9 per cent) it was reduced to nearly normal; and in 4 (17 per cent) hypertension persisted. Comment should be made on the 2 patients whose blood pressure was reduced to nearly normal. One had bilateral disease with severe stenosis on the right and only minimal disease on the left. The lesion on the right was resected 8 years ago, and repeated arteriograms have shown no progression of the disease on the left. Home readings of arterial pressure average approximately 155/95 mm. Hg and are, therefore, much reduced from the preoperative blood pressure average of 216/123 mm. Hg. The second patient (No. 24), who had a bypass aorta–renal artery graft, had a good response to treatment, but her arterial pressure is slightly elevated for her age of 21 years.

Discussion

This description of the clinical, radiographic, and pathologic features of subadventitial fibroplasia suggests that it is a distinct arterial lesion unrelated to the other fibrosing nonatherosclerotic renal arterial diseases. The term "fibromuscular hyperplasia" has been widely used to denote these fibrotic diseases, but we have recently shown that there are four separate lesions within this broad grouping; these are intimal fibroplasia, medial fibroplasia, fibromuscular hyperplasia, and subadventitial fibroplasia.

In our original descriptions of renal arterial disease, subadventitial fibroplasia was called mural fibrosis or scarring. More recently, Wellington[3] gave a clear description of it, but thought it to be a variant of fibromuscular hyperplasia; several other reports[4,10-12] have contained characteristic photomicrographs, also as examples of fibromuscular hyperplasia. This lesion is not fibromuscular hyperplasia, since it is

distinctly different from it in several ways. The hallmark of subadventitial fibroplasia is the thick collagenous collar which can be so extensive that it nearly replaces the media the muscle bundles sometimes seen within the collagen do not represent muscular hyperplasia but are either displaced medial fibers or longitudinal muscle of the adventitia. In contrast, fibromuscular hyperplasia is a diffuse mixture of fibrous and muscular tissue and there is no clear-cut zone of fibrous tissue peripherally. Other distinguishing features concern the intima and *elastica interna*. In subadventitial fibroplasia there may be a small amount of intimal fibroplasia, but the *elastica* is unaffected. Intimal fibroplasia has not been found in fibromuscular hyperplasia; the *elastica interna* is often missing in the juvenile type of this lesion and in the adult type it can be disrupted permitting formation of dissecting aneurysms.

Arteriograms also show a clear difference between these two lesions. Subadventitial fibroplasia rarely affects the proximal segment of the renal artery whereas fibromuscular hyperplasia usually does. The former produces variably severe stenosis, with segments of intense narrowing alternating with segments less narrowed. The latter has two arteriographic patterns depending upon the presence or absence of dissection: without dissection, a symmetrical stenosis with poststenotic dilation is seen, and with dissection the artery is irregularly dilated with the dilatation sometimes overriding the stenosis and obscuring it.

Subadventitial fibroplasia is also clearly separate from medial fibroplasia, both in pathologic and arteriographic characteristics. Medial fibroplasia is the lesion that produces the "beaded" renal artery which some consider to be typical of fibromuscular hyperplasia.[17] The aneurysmal dilatations that produce the "beads" represent areas in which intima, *elastica interna*, and media are missing and the integrity of the vessel is supplied only by the adventitia. The media between the aneurysms is usually largely replaced by collagen interspersed among the muscle fibers. This replacement produces thickened ridges. This diffuse medial infiltration of collagen in medial fibroplasia is completely different from the localized deposition characteristic of subadventitial fibroplasia.

On arteriograms, these lesions also are different (Fig. 3). Both could be thought of as producing "beads"; however, in the case of medial fibroplasia the "beads" represent aneurysms whereas in that of subadventitial fibroplasia they reflect areas in which the stenosis is less intense than proximally and distally. The "bead" of medial fibroplasia is wider than the unaffected artery proximally, whereas the "bead" of subadventitial fibroplasia is the same width or narrower.

Information available from this study gives no indication of the cause of subadventitial fibroplasia. The possibility of flexion stress is suggested because of the location of the lesion in the outer portion of the artery. Furthermore, recent reports[-14] have considered ptosis of the kidney with stretching of the renal artery as a possible factor in the pathogenesis of fibrosing nonatherosclerotic renal arterial lesions. However, it is hard to judge this possibility in regard to subadventitial fibroplasia because the lesions were not subdivided into various types but were classified as fibromuscular hyperplasia. Since we did not use upright intravenous urography or arteriography in our study, we have no indication of the frequency of ptosis in these patients.

Another possible cause of subadventitial fibroplasia is inflammation. This seems to be unlikely because of the rarity of thrombosis, which is a frequent accompaniment of arteritis, and because the earliest lesion that we have seen (Fig. 8 A and B) was unassociated with inflammatory changes. Although this study does not indicate the cause of the lesion, it does suggest that the fibroplasia originates in the *elastica externa*.

In most of these patients revascularization operations seemed to be indicated but these posed difficult technical problems because of the length of stenosis and its proximity to, or involvement of, the primary arterial branches. These difficulties are reflected in the numbers of complications that occurred.

When the lesion is to be excised, excision must be complete; otherwise, stenosis can recur at the suture line, as happened in Patients No. 16-19. In 4 patients (Nos.

19-21, 25) the stenosis was so long that much of the renal artery had to be removed and some type of graft used. In 3 patients, vein grafts were inserted; in the fourth, a splenic artery autograft was made. One of these patients (No. 19) had a return of hypertension with recurrence of stenosis of the proximal suture line, possibly because the lesion had not been completely resected. Another patient (No. 20) died 7 days after operation from hemorrhage when the proximal suture line of an ovarian vein graft ruptured. It seems to be likely that a stronger type of graft should have been used.

In Patient No. 23, failure of the hypogastric artery as a bypass graft may have been related to the presence of disease in the primary arterial branches, the severity of which was not recognized preoperatively.

Splenorenal anastomosis was unsuccessful in the 2 patients in whom it was used. Both patients were operated upon during the early years of experience with this type of renal arterial disease. In one (No. 26), the anastomosis was made in the distal portion of a diseased renal artery, and in the other (No. 27), severe spasm of the splenic artery probably was the cause of the thrombosis that developed. The failure of splenorenal anastomosis in these patients should not be taken to be a general indictment against this procedure, for it has been used successfully as a bypass operation in over 20 other patients with renal arterial stenosis.

Summary

Subadventitial fibroplasia was found to be the cause of renal arterial stenosis in 31 patients operated upon for the relief of hypertension. Twenty-six were females, although they ranged in age from 14 to 48 years, 21 were between 20 and 40 years. The 5 males were from 14 to 40 years of age.

Microscopic examination of arterial segments showed the lesion to be made up of a dense collar of collagen located in the periphery of the media, which was often thinned and disorganized by the fibrous tissue. There was no muscular hyperplasia, but islands of smooth muscle dislocated from either the media or adventitia were sometimes seen to be trapped in the collagen. Occasionally, a small amount of intimal fibroplasia was seen; the *elastica interna* was intact, and dissecting aneurysms were never found.

Renal arteriography showed subadventitial fibroplasia to be a severely stenosing lesion of variable length. Often multiple stenoses of varying severity were seen, and these produced a "beaded" renal artery. The "beads" were not aneurysmal in nature, as is characteristic of medial fibroplasia, a lesion previously called fibromuscular hyperplasia. The right renal artery was affected in 16 patients, and the left one was affected in 7; 8 patients had bilateral disease.

Operations performed were nephrectomy or procedures designed to remove or bypass the stenosis. These treatments were marked by an unusual number of complications and by excellent responses of the blood pressure in most patients in whom the operations were technically successful.

Immediate complications were hemorrhage and thrombosis. Fatal hemorrhage occurred in one patient because of disruption of the suture line of a vein graft. Thrombosis developed in 6 patients. Two patients with single kidneys died of renal failure; another with a single kidney underwent thrombectomy within a few hours, but renal function was never fully recovered. In the other 3 patients, nephrectomy was performed. Stenosis recurred in 4 patients 3 months to 3 years postoperatively.

The response of arterial pressure to treatment could be judged in 23 of the 31 patients. In 17 (74 per cent), hypertension remitted; in 2 (9 per cent), blood pressure was reduced to nearly normal levels; and in 4 (17 per cent), hypertension persisted.

Subadventitial fibroplasia seems to be a disease that frequently affects young women and frequently the right renal artery. It is one of the fibrosing, nonatherosclerotic renal arterial lesions, which have all previously been classified under the general heading of "fibromuscular hyperplasia."

We wish to thank Dr David Humphrey and Dr Ray Gifford, of the Department of Hypertension and Renal Disease, Dr. A. W. Humphries, of the Department of Vascular Surgery, and Dr. Bruce Stewart, of the Department of Urology, for their contributions to the investigation and treatment of some of these patients. We also wish to thank Miss Enid Davy, Miss Rosemarie Horvath, and Miss Christine Monroe for skillful assistance.

Appendix: Complications of renal arterial surgery

Excision with end-to-end anastomosis

PATIENT 14. This patient was first seen here at the age of 19 because of acute ulcerative colitis for which total colectomy was performed. Arterial pressure was normal. Three and one-half years later she returned because of severe hypertension, known for 6 months, which was associated with malignant hypertensive retinopathy. Renal arteriography showed narrowed right renal artery, very atrophic right kidney, and minimal disease of the left main renal artery. Right nephrectomy was performed; hypertension and retinopathy disappeared. Eleven months after nephrectomy, she became acutely ill with sudden pain in the left flank, oliguria, severe hypertension, and azotemia. She was transferred to this hospital and operated upon 2 days after the onset of the acute illness. The left renal artery contained thrombus, which was removed; diseased segment of the artery was excised, and an end-to-end anastomosis performed. After this, the urinary output rose promptly and the azotemia cleared. Two weeks after thrombectomy severe oliguria suddenly recurred. She was operated upon again, and again the renal artery contained a thrombus. This was removed, and the artery was widened with a patch graft. Two hemodialyses were required in the first week after operation, but thereafter renal function returned slowly and hypertension remitted.

During the next 10 months, hypertension did not recur; however she had severe recurrent infections of the urinary tract, progressive azotemia, thrombophlebitis, pulmonary emboli, and, finally, necrotizing enteritis which caused her death.

PATIENT 15. This 43-year-old woman had known of hypertension 14 years prior to discovery of renal arterial stenosis in the mid-portion of the larger of two right renal arteries. Excision was performed, but occlusion of the artery occurred postoperatively. Right nephrectomy was performed 1 year later but hypertension did not remit.

PATIENT 16. This young woman had disease of the distal two thirds of the right renal artery, which was excised. Her arterial pressure was normal for 2 years postoperatively, but by the third year hypertension had returned and stenosis at the site of anastomosis was found. An attempt to excise the stenotic segment failed, and nephrectomy was performed.

PATIENT 17. This woman underwent an excision of lesion affecting the distal portion of the right renal artery. Three years later hypertension returned and stenosis at the suture line was found. Another excision was carried out, but restenosis occurred as shown by arteriography performed 4 and 19 months postoperatively. She was given guanethidine for control of hypertension, but eventually stopped taking it several months later her blood pressure was 160/80 mm Hg.

PATIENT 18. This woman had stenosis of the middle third of the right renal artery which was excised. Hypertension, which remitted promptly postoperatively, returned in 4 years. Arteriography showed stenosis at the bifurcation of the right renal artery. At the second operation the stenotic bifurcation was widened by the use of a Y-shaped elastic patch graft. After this, her hypertension once more disappeared.

Excision and insert vein graft.

PATIENT 19. This woman had fibroplasia of the distal half of the right renal artery. The segment was excised and replaced by an ovarian vein graft. Arterial pressure became normal and remained so for the next 3 months, and then began to rise again. Six months after operation, arteriography showed stenosis at the proximal suture line. A second operation was followed by thrombosis of the renal artery and nephrectomy was performed; arterial pressure has been normal during the subsequent 3 years.

PATIENT 20. This woman had a severely stenotic lesion of the mid and distal portions of the right renal artery which was excised. The length of the segment removed precluded end-to-end anastomosis, and an ovarian vein graft was used. She died 7 days after operation, from hemorrhage when the proximal suture line ruptured.

Bypass arterial grafts.

PATIENT 22. This 19-year-old young man had lesion of the proximal segment of the left renal artery. This was bypassed by an arterial homograft that was connected to a short segment of aortic homograft. The arterial graft occluded soon after operation, and nephrectomy was performed. Diastolic hypertension remitted.

PATIENT 23. This 27-year-old woman had been known to be hypertensive for 18 years. The left kidney had been removed because of hydronephrosis and chronic pyelonephritis. Eight years later she was found to have severe stenosis of the distal portion of the right renal artery. Through use of the hypogastric artery, an aorta-renal artery bypass graft was inserted. Two days postoperatively occlusion of arterial branches occurred, resulting in extensive renal infarction and renal failure. The kidney was removed and two kidney transplants from cadaver were subsequently used; both failed and the patient died.

Splenorenal arterial anastomosis.

PATIENT 26. This 17-year-old boy with bilateral renal arterial stenosis had undergone right nephrectomy because an arterial reconstructive operation had failed. The lesion on the left involved the distal arterial segment and branches. A splenorenal arterial anastomosis was performed but the kidney failed to function postoperatively and the patient died of renal failure. Although renal arteriography was not performed and autopsy permission was refused, it seems to be likely that thrombosis had occurred.

PATIENT 27. This 14-year-old girl had stenosis of the proximal portion of the right renal artery. The artery was transected distal to the lesion and anastomosed to the splenic artery, which had been mobilized and swung to the right side. During the procedure, the splenic artery went into severe spasm and thrombosis occurred.

REFERENCES

1. McCormack, L. J., Poutasse, E. F., Meaney, T. F., Noto, T. J., Jr., and Dustan, H. P.: A pathologic-arteriographic correlation of renal arterial disease, Am. Heart J. 72: 188, 1966.
2. McCormack, L. J., Hazard, J. [illegible]

E. F Obstructive lesions of the renal artery associated with remediable hypertension Am. J Path 34:587 1958.
3 McCormack, L. J Vascular changes i hypertension, M. Clin North America 45:247 1961
4. Wylie, E. J and Wellington, J S. Hypertension caused by fibromuscular hyperplasia of the renal arteries Am. J Surg 100 183 1960.
5 Wellington J S. Fibromuscular hyperplasia of renal arteries in hypertension, Am. J Path. 43:955 1963
6. Poutasse, E. F Diagnosis and treatment of occlusive renal artery disease and hypertension, J A M.A 178 1078, 1961
7 Meaney T F and Dustan H. P Selective renal arteriography i the diagnosis of renal hypertension, Circulation 28 1035 1963
8. Dustan, H P Poutasse, E F Corcoran, A. C., and Page, I H. Separated renal f nctions in patients with renal arterial disease, pyeloneph ritis, and essential hypertension, Circulation 23:34 1961
9 *Dustan, H P Page I H Poutasse, E. F* and Wilson L. A evaluation of treatment of hypertension associated w th occlusive renal arterial disease, *Circulation 27 1018, 1963*
10. DeCamp, P T and Birchall, R : Recognition and treatment of renal arterial stenosis associated with hypertension, Surgery 43:134 1958.
11 Perloff D Sokolow M Wylie, E. J Smith, D R., and Palubinskas, A. J : Hypertension secondary to renal artery occlusive disease Circulation 24 1286, 1961
12 Wylie, E. J Perloff D and Wellington, J Fibromuscular hyperplasia of the renal arteries, Ann. Surg 156:592 1962.
13. Palubinskas, A. J and Wylie, E. J : Roentgen diagnosis of fibromuscular hyperplasia of the renal arteries, Radiology 76:634 1961
14 Kaufman, J J nd Hughes, D L.: Upright aortography: an aid to the study of renal artery stenosis, Radiology 79 1017 1962.
15. Kaufman J J and Maxwell, M H.: Upright aortography in the study of nephroptosis, *stenotic lesions of the renal artery* and hypertension, Surgery 53 736, 1963.
16. Kaufman J J Hanafee, W nd Maxwell, M H *Upright renal arteriography in the* study of renal hypertension, J.A.M.A. 187:87 1964.

The malformation complex of the absence of the arch of the aorta—Steidele's complex

J. T. Lie, M.B., B.S.
Melbourne, Australia

Congenital malformations of the heart account for a considerable number of neonatal deaths. In the state of Victoria, Australia, the predominant type of congenital cardiac anomaly found at neonatal autopsy is transposition of the great vessels, which is followed in frequency by ventricular septal defect, coarctation of the aorta, and atresia of the aortic valve. This is in agreement with experiences reported from North America.[1-4]

Absence of the arch of the aorta is one of the least common congenital cardiac anomalies. It was not listed as an entity in a series of 6,053 infants born with malformations of the cardiovascular system reviewed by Richards and associates. Among the case reports, Evans[7] found 3 patients with this anomaly in 19,417 autopsies at the London Hospital, and the case described by Hamburger was at that time the only one in 15,000 autopsies performed at the Johns Hopkins Hospital.

Recently, within a short period of 5 weeks, this anomaly was seen in 2 newborn infants at Footscray and District Hospital.† In each case absence of the arch of the aorta was accompanied by patent ductus arteriosus, ventricular septal defect, valvular incompetent foramen ovale, subaortic stenosis, and bicuspid aortic valve. It is the purpose of this communication to describe these 2 new cases, to review briefly the literature on the subject, and to propose a uniform terminology for this type of malformation complex.

Clinical records

Case 1 (FDH 73931). A female infant was delivered on May 7, 1964, 4 days before the expected date. The delivery was normal and the infant weighed 2,550 grams at birth. Shortly after birth it was noted that the infant cried feebly and had a marked grayish pallor. The pallor persisted over the next 2 days and appeared to be worse whenever she was handled. She took her feeding slowly and readily became exhausted. On the fourth day differential cyanosis was noted for the first time, being confined to the abdomen and the lower extremities. In addition, she had a tachycardia and became very dyspneic. She was given oxygen and was fully digitalized, but she died soon afterward. The final clinical diagnosis was congestive cardiac failure due to congenital heart disease.

There was no family history of congenital heart disease. The mother, 22 years old, had one living and normal child, born 2 years previously. During the early part of her present pregnancy she had taken some drugs (presumably abortients) but the identity of which was never revealed when her menstrual period was 2 weeks overdue. Her action did not produce the desired effect and the pregnancy continued uneventfully until the time of delivery.

Autopsy was performed on the body of the female infant, which weighed 500 grams and measured 43 cm in length. No abnormality was noted externally. The pericardium and the pleurae were thin ... [illegible]

From the Department of Clinical Pathology, Royal Melbourne Hospital, Melbourne, Australia.
Received for publication June 30, 1964.
*Formerly Registrar, Department of Pathology, Footscray and District Hospital, Victoria, Australia. Present address: Department of Clinical Pathology, Royal Melbourne Hospital, Grattan St., Parkville, N., Victoria, Australia.
†Footscray and District Hospital [illegible] ... beds, of which 38 beds are allocated to obstetric patients. The annual average number of births [illegible] ... 000 to [illegible] 900.

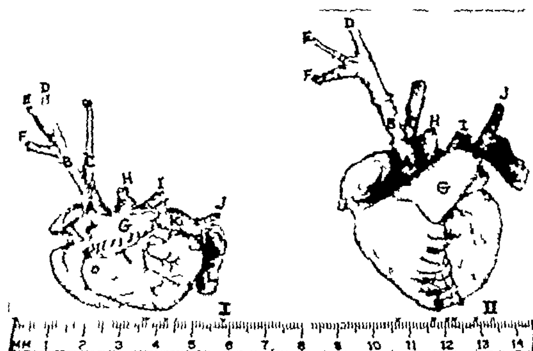


Fig. 1. Autopsy specimen displaying the vessels leaving the heart. *A*, Ascending aorta. *B*, Innominate artery. *C*, Left common carotid artery. *D*, Right common carotid artery. *E*, Right vertebral artery. *F*, Right subclavian artery. *G*, Pulmonary trunk. *H*, Right pulmonary artery. *I*, Left pulmonary artery. *J*, Left subclavian artery. *K*, Ductus arteriosus. *L*, descending aorta.

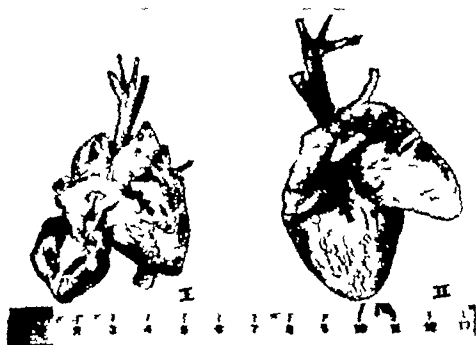


Fig. 2. Opened hearts display the ventricular septal defect, as indicated by the arrow.

The lungs were markedly congested. The venous return to the heart was normal. The heart was considerably enlarged and globe shaped. The right atrium and the tricuspid valve were normal but there was a valvular incompetent foramen ovale. The right ventricle was hypertrophied and dilated. The pulmonary trunk was also dilated. It arose from the right ventricle, and after branching off the right and left pulmonary arteries, it continued as the descending aorta via a widely patent ductus arteriosus. A oval defect, 4 by 6 mm. was present in the membranous portion of the ventricular septum. The aortic valve was bicuspid and there was subaortic stenosis. The aorta, less than one half of the caliber of the pulmonary trunk, originated from the left ventricle and ended by dividing into the innominate artery and the left common carotid artery. A vessel arising from the ductus arteriosus took the course of the left subclavian artery. There was no connection of any kind between the ascending aorta and descending aorta (Figs. 1 and 2).

Case II (FDH 7307-I). A female infant was delivered on March 31, 1964, 12 days after the expected date. The delivery was normal and the infant weighed 2,900 grams at birth. The condition of the infant at birth and shortly afterward was satisfactory and no cyanosis was noted. On the sixth day she developed tachycardia and dyspnea, and a loud "to-and-fro" murmur was heard in the second left intercostal space. A chest x-ray film was obtained and showed gross cardiac enlargement (Fig. 3). She did not respond to oxygen and digitalization and died 6½ hours later. The final clinical diagnosis was congestive cardiac failure due to congenital heart disease.

There was no family history of congenital heart disease. The mother, 28 years old, had had a miscarriage at the eleventh week of gestation some 15 months previously. During the first half of her present pregnancy she received weekly intramuscular injections of hydroxyprogesterone caproate, 250 mg.



Fig. 3. Case II. Posteroanterior chest x-ray film demonstrates the cardiomegaly.

In addition, she was also given thyroxine, 0.1 mg. daily throughout the pregnancy because of a clinical diagnosis of hypothyroidism.

Autopsy was performed on the body of the female infant. It weighed 2,750 grams and measured 48 cm. in length. As in Case I, the relevant findings were limited to the thorax.

The lungs were markedly congested. The heart was grossly enlarged, chiefly because of hypertrophy of the right ventricle. The venous return to the heart was normal. A dilated pulmonary trunk emerged from the right ventricle and after supplying the right and left pulmonary arteries, continued as the descending aorta via a patent ductus arteriosus. The aorta originated from the left ventricle and ended by dividing into the innominate and the left common carotid arteries. The left subclavian artery arose as a separate vessel from the ductus arteriosus. There was no connection of any kind between the ascending aorta and the descending aorta (Fig. 1).

The opened heart revealed a dilated right atrium with a normal tricuspid valve and a valvular incompetent foramen ovale. There was a defect 5 mm. in diameter in the membranous portion of the ventricular septum (Fig. 2). The left atrium and the left ventricle were slightly dilated. The aortic valve was bicuspid and there was subaortic stenosis. The pulmonary and mitral valves were normal.

Definition and classification

Absence of the arch of the aorta means that there is no connection of any kind between the ascending aorta and the descending aorta, the latter being the continuation of the pulmonary trunk via a patent ductus arteriosus. Functionally it corresponds to the most severe form of infantile type (preductal) coarctation. The lower part of the body and varying portions of the upper part of the body receive their supply of blood from the right ventricle through the "pulmonary-ductus-descending aorta," a term first introduced by Evans.

Interruption of the arch of the aorta may occur at any point between the embryonic aortic sac and the ductus arteriosus. In 1927 Abbott described two types of this anomaly. They were interruption of the arch of the aorta distal to the origin of the left subclavian artery (Fig. 4,*A*) and interruption distal to the origin of the left common carotid artery with the left subclavian artery arising from the descending aorta (Fig. 4,*B*). In both instances, the pulmonary trunk, after giving off the right and left pulmonary arteries, continues as the descending aorta via a patent ductus arteriosus. A third variety was first reported by Weisman and associates,

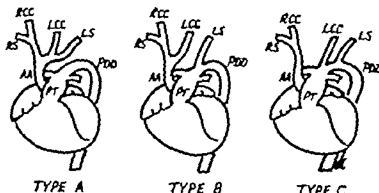


Fig. 4. Schematic illustrations of the three basic types of the absence of the arch of the aorta. *AA* Ascending aorta. *LCC* Left common carotid artery. *LS* Left subclavian artery. *PDD* Pulmonary-ductus-descending aorta trunk. *PT* Pulmonary trunk. *RCC* Right common carotid artery. *RS* Right subclavian artery.

which the interruption of the arch of the aorta is distal to the origin of the innominate artery and both the left common carotid and the left subclavian arteries arise from the descending aorta (Fig. 4 *C*). These three anatomic variants of the absence of the arch of the aorta have been referred to as Types A, B, and C by Celoria and Patton and represent progressively more severe degrees of the malformation complex.

Blake and associates[12] considered this simple classification to be inadequate. They pointed out that by employing the concept of double aortic arch described by Edwards[13] one could distinguish nine different varieties of interruption of the arch of the aorta. Many such cases have in fact been reported in the literature.[14-18] However, they were only examples of the above mentioned three basic types, with additional features derived from the persistence of the right fourth and sixth aortic arches and the right-sided dorsal aorta. Roberts and associates,[1] for instance, have found that the classification of absence of the arch of the aorta into Types A, B, and C is applicable to every one of the 58 documented cases reviewed by them.

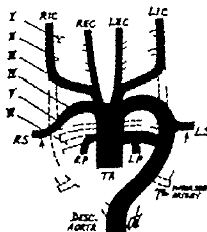


Fig. 5. A schematic representation of the development of the aortic arches. The Roman numerals designate the six pairs of embryonic aortic arches; the broken lines represent vestigial vessels; and the arrows indicate the cranial migration of the subclavian arteries after the seventh week. *LEC*, Left external carotid artery. *LIC*, Left internal carotid artery. *LP* Left pulmonary artery. *LS* Left subclavian artery. *REC*, Right external carotid artery. *RIC*, Right internal carotid artery. *RP* Right pulmonary artery. *RS* Right subclavian artery. *TA* Truncus arteriosus.

Pathogenesis

Absence of the arch of the aorta, despite its apparent variability and complexity, can be resolved to a common developmental basis. When one studies the diagram of Rathke or some modification of it (Fig. 5), it would seem to be obvious that the anomalies result from alterations in the process determining normal differentiation in a circumscribed region of the embryonic aortic arch system beginning at a fairly definite time in development. The region in question includes the fourth and sixth arches, and the contiguous portions of the two dorsal aortas and the ductus arteriosus. With regard to the time factor, it should be

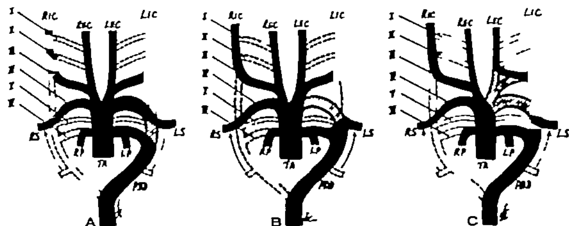


Fig 6 Schematic representation of the embryonic aortic arches and their development. The lined areas indicate the sites at which regression or atresia would result in the three basic types (A, B and C) of absence of the arch of the aorta. (See Fig 5 for key to the diagrams.)

recalled that, in human embryos, the differentiation of the fourth and sixth arches, the partition of the truncus arteriosus, the formation of interventricular septum and the caudal descent of the heart all take place in the second month of gestational age.

Type A malformation represents a regression or atrophy of the arch of the aorta between the ductus and the left subclavian artery (Fig 6,*A*) The regression appears to have taken place after the seventh week of the embryonic life when the normal processes of caudal descent of the heart and the cranial migration of the seventh intersegmental artery have been completed. Type B malformation appears to have resulted from the failure of the development of the left fourth aortic arch before the seventh week of embryonic life since the left subclavian artery remains with the descending aorta (Fig 6,*B*)

The pathogenesis of Type C malformation is more complex. Celoria and Patton suggested two possibilities a partial or complete failure of formation of the left third and fourth aortic arches, with persistence of the segment of the left dorsal aorta between these two arches or failure of connection of the aortic sac with the left third and fourth aortic arches, and the fusion of these two arches to form the left common carotid artery (Fig 6,*C*) The time factor is also more difficult to ascertain but appears to be very early in embryonic life probably in the fifth or sixth weeks of gestation.

Discussion

The mechanisms by which certain of the embryonic aortic arches regress while others persist and develop into the main channels in the definitive pattern of the great vessels have been elucidated by Congdon[22] and Barry[8] In the fetus although the division of the current of blood which supplies the head and the upper extremities occurs between the third and fourth aortic arches, almost the entire output of the right ventricle is carried into the descending aorta via the ductus arteriosus, whereas a considerable proportion of the left ventricular output goes to the carotid arteries before reaching the narrow isthmus aortae (Fig 7 A) Thus a pulmonary ductus-descending aorta trunk is already in existence and functioning

The lumen of the ductus arteriosus is occluded postnatally by an overgrowth of its intimal tissue and as the ductus closes, all the blood entering the descending aorta must traverse the arch of the aorta and the isthmus is slowly widened (Fig 7,*B*) It is usually 3 to 4 months after birth before all traces of the narrowing of the isthmus aortae have entirely disappeared[23] If however there is a delay in the development and fusion of the truncoconal ridges dividing the truncus arteriosus with the caudal descent of the heart the angle between the

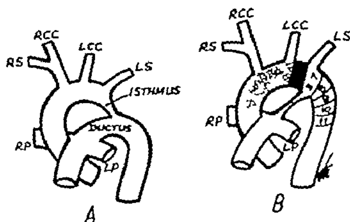


Fig 7 The configuration of the ar h of aort t birth (A), nd 3 t 4 months after birth (B). The stippled area indicates the segment of the entr l aorta between the fourth and sixth arches the black rea indicates the left fourth aortic arch and the Arab numerals indicate the segmentally arranged dorsal aortic roots.

outgrowth of the aortic sac and the aortic arches will be such as to direct the outflow of blood into the more proximal and posterior sixth arch The same delay or mal development may also result in incomplete division of the truncus arteriosus malformation of the valve cusps and ventricular septal defect [19] These changes will greatly accentuate the difference in the volume of flow between the isthmus aortae and the ductus arteriosus and encourage the persistence of the pulmonary-ductus-descending aorta trunk after birth The frequent association of absence of the arch of the aorta with hypoplasia of the ascending aorta bicuspid aortic valve and subaortic stenosis lends support to the explanation outlined above.

The etiological factors responsible for most congenital malformations are complex and have not been clearly established It has been estimated that about 10 per cent of these malformations are associated with known genetic factors and perhaps 1 per cent with environmental factors such as maternal rubella ingestion of drugs and irradiation. However any one of the known factors may influence or interact with one or more of the others in producing a certain malformation or a group of congenital defects.

With regard to the absence of the arch of the aorta, one is impressed by the absence of any proposal of possible etiological factors in all of the reported cases in the literature. However this is hardly surprising in view of our almost total ignorance of the subject matter In the 2 cases described in this paper one can do no more than speculate on the significance of the administration of drugs to the mothers in the early stages of their pregnancies. It is extremely difficult to establish a satisfactory correlation between the taking of a drug by the expectant mother and the birth of a deformed child unless the effect of the drug is very specific and pronounced The interpretation of the results of experiments on laboratory animals is also subject to many pitfalls [21] Nevertheless, some years ago Wilson and Warkany[22] revealed very interesting observations concerning the aortic arch and intracardiac anomalies in the offspring of rats deficient in vitamin A. Among the 64 malformed animals studied 22 (34 per cent) exhibited anomalies of the aortic arch and a ventricular septal defect was also present in 16 of these 22 animals (73 per cent) Furthermore 3 rat fetuses had the malformation complex of absence of the arch of the aorta patent ductus arteriosus and ventricular septal defect, similar to the three types described in this paper To my knowledge these were the only examples of experimentally produced absence of the arch of the aorta reported to date. The question by what means is maternal vitamin A deficiency able to alter the normal development of the fetal heart and the great vessels, remains unanswered

Incidence Raphael Steidele Professor of

Table I. Reported cases of absence of the arch of the aorta

Author and Year	Number of cases	Sex	Age when diagnosed	Type	VSD	ASD
Roberts et al.[13] (1962)	58	M (23) F (27) ? (8)	Stillborn to 14 years 42 died in first month 7 lived over 1 year	A (22) B (29) C (2)	49/51	31
Tiedmann[20] (1831)	1	M (1)	9 days	B (1)	1	1
Preisz[22] (1890)	1	F (1)	? days	B (1)	1	1
Blake et al.[18] (1962)	18	M (9) F (6) (3)	Stillborn to 20 months 14 died in first month 1 lived over 1 year	A (9) B (8) C (1)	17/18	16
Mehrizi and Morrish[20] (1962)	6	M (4) F (2)	2 days to 2 years 4 died in first month 1 lived over 1 year	A (4) B (2)	4/6	3
Solla[20] (1964)	1	F (1)	3 days	B (1)	1	1
Pillsbury et al.[20] (1964)	1	F (1)	16 years	C (1)	—	—
Morgan et al. (1965)	1	M (1)	6 days	A (1)	1	—
Steiner and Finegold[20] (1965)	1	M (1)	2 months	B (1)	1	—
Present series	2	F (2)	4 days and 6 days	B (2)	2	2
Total	90	M (39) F (40) ? (11)	Stillborn to 16 years 66 died in first month 10 lived over 1 year	A (36) B (45) C (4) (5)	77/83	55

*Including the case previously reported by Hamburger[4] and reviewed by Roberts and associates.[1]
VSD: Ventricular septal defect. ASD: Atrial septal defect or valvular incompetent foramen ovale.

Obstetrics at the University of Vienna, was the first to record a case of congenital absence of the arch of the aorta in the late eighteenth century. His patient, a newborn infant (sex not stated) had a Type A malformation and lived for a few hours only. Since then sporadic case reports continue to appear in the literature. In 1962 Roberts and his associates[1] reported detailed clinical, angiographic, hemodynamic, and pathologic studies of 3 patients seen at the National Health Institute. They also reviewed all but 2 documented cases[4-27] up to that time. In the same year Blake and associates[18] reported 18 cases registered at the Armed Forces Institute of Pathology, and Mehrizi and Morrish[18] described 7 cases from the Johns Hopkins Hospital (including 1 case previously reported by Hamburger[4]). Since 1962 at least 4 new cases have appeared in the literature.[20-23] Thus, with the cases reported in this paper it would appear that to date only 90 cases of absence of the arch of the aorta have ever been recorded (Table I).

Clinicopathologic data. The sex of the 90 patients was mentioned in 79 instances; there were 39 males and 40 females. The site of the interruption of the arch of the aorta was clearly described in all but 5 cases: type A was found in 36 patients (40 per cent), type B in 45 patients (50 per cent), and type C in 4 patients.

Absence of the arch of the aorta seldom if ever occurred as an isolated malformation. In all but 1 case, that reported by Pillsbury and associates,[20] there was a patent ductus arteriosus. A ventricular septal defect was also present in 77 of the 83 cases (93 per cent) in which the septum was mentioned. An atrial septal defect or a valvular incompetent foramen ovale was seen in 55 cases (60 per cent). Other additional congenital cardiac anomalies included hypoplastic aorta, bicuspid aortic valve, subaortic stenosis, persistent truncus arteriosus, transposition or corrected transposition of the great vessels, bila

ductus arteriosus the right subclavian artery arising from the descending aorta biventricular origin of the pulmonary trunk, persistent ostium atrioventriculae commune, and aorticopulmonary window According to Mehrizi[33] interruption of the arch of the aorta is also frequently associated with origin of both vessels from the right ventricle without pulmonary stenosis.

Sixty-six of the 90 patients (73 per cent) died in the first year of life or were still born. Pulmonary hypertension and congestive cardiac failure were the cause of death in most instances. Only 10 patients lived longer than 1 year at the time of their reports. The oldest and living patient reported on[36] a 16-year-old girl was a unique case in many ways. She had a type C malformation which was not associated with other intracardiac anomalies, nor was a patent ductus arteriosus demonstrated The flow of blood to the descending aorta was by way of collateral vessels in the right side of the chest wall and by retrograde flow in the left common carotid and the left subclavian arteries. The patient complained of no significant symptoms until the age of 16 A successful surgical correction was accomplished by restoring the continuity between the ascending and descending aortas by means of a Dacron graft

Contrary to what has been stated and emphasized[33] differential cyanosis was the exception rather than the rule in the reported cases The infrequent occurrence of differential cyanosis can be attributed to the presence of a large left to-right shunt that resulted in adequate oxygen saturation of blood in the descending aorta

A clinical diagnosis of the absence of the arch of the aorta is extremely difficult, if not impossible to make The associated cardiac anomalies tend to overshadow and confuse the true picture of the interruption of the arch of the aorta. The peripheral pulse is of good quality and of equal strength in the arms and there is no diminution in the femoral pulsations. A systolic murmur and a thrill if present, probably originate from the ventricular septal defect and the subaortic stenosis The chest x-ray film may reveal cardiac enlargement and evidence of a large left to-right shunt. The standard leads of the electrocardiogram usually show right axis deviation and right ventricular hypertrophy Diphasic QRS complexes of high voltage over the right and left precordia have also been described as being indicative of combined ventricular hypertrophy

Cardiac catheterization selective angiocardiography and aortography are necessary to demonstrate the entire malformation complex. Aortography is best performed through the right brachial artery The preparation and dosage used must be those suitable for cerebral angiography because the major part of the injected material inevitably goes to the brain.[33]

It is not surprising therefore, that only 14 of the 90 documented cases (17 per cent) of absence of the arch of the aorta were diagnosed in living patients (Table II)

Despite the notoriously high mortality rate associated with this malformation complex in early infancy complete interruption of the arch of the aorta is amenable to surgery usually in the form of placement of a prosthetic graft between the ascending and descending aortas combined with the division of the ductus arteriosus. To date there have been 8 attempts at surgical correction in 2 of these cases the patients died before the procedure could be completed As to the other 6 attempts, 4 were successful (Table II) The limiting factors appear to be the severity of the additional cardiac anomalies and the early recognition of the precise nature of the malformation complex.[34]

A uniform terminology—Steidele's complex? To date absence of the arch of the aorta has been known under various other names the variability of terminology that one encounters in the literature is matched only by the complexity of the malformation itself This lack of a uniform terminology greatly hampers the task of collecting data which is so essential for the better understanding of a difficult problem.

The most commonly employed synonym is interruption (or atresia) of the aortic arch (or isthmus) However the absence of the arch of the aorta was often not mentioned at all in the title of a case report[17,20,34] or was regarded as being coarctation of the aorta.[37]

The constant association of the absence of the arch of the aorta with patent ductus

Table II Cases diagnosed in living patients and attempts at surgical correction

Patient	Author and Year	Sex	Age	Type	Method of diagnosis	Surgical correction	Result
1	Dorney et al.[46] (1955)	F	5 yr	B	Thoracotomy	Not attempted	—
2	Merrill et al.[a] (1957)	F	3½ yr	A	Thoracotomy	End-to-side anastomosis of left subclavian artery to descending aorta	Successful
3	Abrams[a] (1958)	F	10 days	A	Angiocardiography	Not attempted	—
4	Quie et al.[42] (1959)	M	5½ mo.	B	Thoracotomy	Left common carotid artery sutured to descending aorta	Died in early postop. period
5	Castellanos et al.[44] (1959)	M	9 yr	A	Angiocardiography	Not attempted	—
6	Ruiz Villalobos et al.[a] (1961)	M	14 yr	A	Thoracotomy	Teflon graft between left subclavian artery and descending aorta	Successful
7	Blake et al.[a] (1962)	M	20 mo.	B	Angiocardiography	Dacron graft between ascending and descending aortas	Successful
8	Roberts et al.[77] (1962)—Case R.S.	M	18 days	A	Angiocardiography	Not attempted	—
9	Roberts et al.[a] (1962)—Case P.S.	F	3 yr	A	Angiocardiography	Teflon graft between ascending and descending aortas	Died in early postop. period
10	Mehrizi and Morrish[a] (1962)—Case V	M	1 mo.	B	Angiocardiography	Procedure not completed	Died during operation
11	Mehrizi and Morrish[a] (1962)—Case VI	M	2½ mo.	A	Angiocardiography	Procedure not completed	Died during operation
12	Mehrizi and Morrish[a] (1962)—Case VII	M	2 yr	A	Angiocardiography	Not attempted	—
13	Pillsbury et al.[a] (1964)	F	16 yr	C	Angiocardiography	Dacron graft between ascending and descending aortas	Successful
14	Morgan et al.[a] (1965)	M	6 days	A	Angiocardiography	Not attempted	—

[a]Patients on whom surgical correction was attempted.

arteriosus and ventricular septal defect has led Everts-Suárez and Carson[19] to suggest that the anomalies should be known as a cardiovascular trilogy. On the other hand Lev[77] and Noonan and Nadas[48] were impressed by the frequent association of obstructive lesions in the left side of the heart with interruption of the arch of the aorta, and so they used the term "the hypoplastic left heart syndrome." Each of these proposals has its merit but falls short in the all-embracing nature intended to accommodate the extreme variations seen among the documented cases of absence of the arch of the aorta.

The term "Steidele's complex" is proposed to honor the man who first described this condition. It has the advantages of distinctiveness, simplicity, and flexibility. The complex can be broadly defined as any congenital cardiac malformation in which there is no connection between the ascending and descending aortas. The classification of cases into types A, B, and C

throughout this paper can be retained in order to indicate the site of interruption

Summary

The malformation complex of the absence of the arch of the aorta is a rare congenital anomaly. Two new cases diagnosed at autopsy have been described together with a brief review of certain clinicopathologic data in 88 other cases reported in the literature.

Developmentally abnormal division of the truncus arteriosus favoring the pulmonary trunk and intracardiac left-to-right shunt are the primary lesions leading to the persistence of fetal ductus function and the regression of the arch of the aorta. According to the site of interruption three basic types (A, B, and C) of absence of the arch of the aorta are recognized. In the great majority of reported cases, the absence of the arch of the aorta is associated with patent ductus arteriosus and a ventricular septal defect. Other additional cardiac anomalies are varied and numerous.

The malformation complex is associated with a mortality rate of 73 per cent in the first year of life; deaths result from pulmonary hypertension and early congestive cardiac failure. Only 14 of the 90 recorded cases were diagnosed in living patients either at exploratory thoracotomy or by angiocardiography and aortography. The defects are amenable to surgical correction and there have been 8 attempts in the past, 4 of which were successful ventures.

The need for a uniform terminology has been stressed and the term "Steidele's complex" is proposed to include all cases of malformation complex in which there is no connection between the ascending and descending aortas.

I am indebted to Dr. Helen Taussig for encouragement and helpful advice in the preparation of this paper.

REFERENCES

1. Consultative Council on Maternal and Perinatal Mortality: Survey of neonatal deaths in Victoria, Annual Report, Department of Health, Victoria, 1962.
2. Consultative Council on Maternal and Perinatal Mortality: Survey of neonatal death, Victoria, Annual Report, Department of Health, Victoria, 1963.
3. Ober, W. B., and Moore, T. E., Jr.: Congenital cardiac malformations in the neonatal period. An autopsy study, New England J. Med. 253:271, 1955.
4. Rowe, R. D., and Cleary, T. E.: Congenital cardiac malformations in the newborn period: Frequency in a children's hospital, Canad. M. A. J. 83:299, 1960.
5. Mehrizi, A., Hirsch, M. S., and Taussig, H. B.: Congenital heart disease in the neonatal period. Autopsy study of 170 cases, J. Pediat. 65:721, 1964.
6. Richards, M. R., Merritt, K. K., Samuels, M. H., and Langmann, A. G.: Congenital malformation of the cardiovascular system in series of 6,053 infants, Pediatrics 15:12, 1955.
7. Evans, W.: Congenital stenosis (coarctation) atresia, and interruption of aortic arch, Quart. J. Med. (N. S.) 2:1, 1933.
8. Hamburger, L. P.: Congenital cardiac malformation presenting complete interruption of the isthmus aortae with transposition of great arteries, Bull. Johns Hopkins Hosp. 61:421, 1937.
9. Abbott, M.: Congenital cardiac disease, Osler: Modern Medicine, Vol 4, ed. 3, Philadelphia, 1927, Lea & Febiger.
10. Wessman, D., Keston, H. D., and Plains, W. I.: Absence of transverse aortic arch with defects of cardiac septums, Am. J. Dis. Child. 76:326, 1948.
11. Celoria, G. C., and Patton, R. B.: Congenital absence of the aortic arch, Am. Heart J. 58:407, 1959.
12. Blake, H. A., Manion, W. C., and Spencer, F. C.: Atresia or absence of the aortic isthmus, J. Thoracic & Cardiovas. Surg. 43:607, 1962.
13. Edwards, J. E.: Anomalies of the derivation of the aortic arch system, M. Clin. North America 32:925, 1948.
14. Edwards, J. E.: Pathology of anomalies of thoracic aorta, Am. J. Clin. Path. 23:1240, 1953.
15. Jew, E. W., Jr., and Gross, P.: Aortic origin of the right pulmonary artery and absence of the transverse aortic arch associated with patency of interventricular septum and ductus arteriosus, Arch. Path. 53:191, 1952.
16. Barger, J. D., Creasman, R. W., and Edwards, J. E.: Bilateral ductus arteriosus associated with interruption of the aortic arch, Am. J. Clin. Path. 24:441, 1954.
17. Becu, L. M., Tauxe, W. N., DuShane, J. W., and Edwards, J. E.: A complex of congenital cardiac anomalies: Ventricular septal defect, biventricular origin of the pulmonary trunk and subaortic stenosis, Am. Heart J. 50:901, 1955.
18. Kleinermann, J., Yang, W., Hackel, D., and Kaufman, N.: Absence of the transverse aortic arch, Arch. Path. 65:490, 1958.
19. Roberts, W. C., Morrow, A. G., and Braunwald, E.: Complete interruption of the aortic arch, Circulation 26:39, 1962.
20. Congdon, E. D.: Transformation of the aortic arch system during the development of the human heart, Contrib. Embryol. 14:47, 1922.

21 Barry A The aortic arch derivatives in the human heart, Anat. Rec. 111:221 1951
22. Patten B. M Human embryology ed. 2 London 1953, J & A. Churchill.
23. Steiner P and Finegold, M J Truncus arteriosus with atresia of the aortic arch Arch Path 79:518, 1965
24 Warburton, D Trasler D G., N lor A. Miller J R nd Fraser F C. Pitfalls in tests for teratogenicity Lancet 2 1116, 1962.
25. Wilson, J G., and Warkany J: Aortic arch and cardiac anomalies in the offspring of vitamin A deficient rats, Am J Anat. 85 113, 1949
26 Tiedmann, F Quoted by Steiner nd Finegold.[23]
27 Preisz, H Quoted by Steiner and Finegold.[23]
28. Mehrizi, A., and Morrish, H F I terruption of the aortic arch, Bull. Johns Hopkins Hosp. 111 127 1962.
29 Solis, J R. Atresia of the aortic arch Report of a case Arch Path. 77:97 1964
30 Pillsbury R. C Lower R R., and Shum y N F Atresia of the aortic arch, Circulation 30 749 1964
31 Morgan A. D Brinsfield, D and Edwards, F K Persistent truncus arteriosus A unusual variant ith atresia of th aortic arch, Am. J Dis Child 109 74 1965
32. Mehrizi, A. Personal communication 1964.
33. Taussig H B Congenital malformations of the heart, Vol. 2, Cambridge 1960. Harvard University Press.
34 T ssig, H B Personal communication 1964.
35. Abrams, H L Persistence of fetal ductus f nction, Circulation 18:206, 1958.
36 Neufeld, H N Ongley P A., Swan, H J C., Burget, E. O J and Edwards, J E. Biventricular origin of the pulmonary trunk with subaortic tenosis abov the ventricular septal defect, Am. Hea t J 61 189 1961
37 Newcombe C. P Ongley P A., Ed ards, J E., nd Wood, E. H Clinical, pathologic and hemodynamic considerations i coarctation of the aorta associated ith ventricular septal defect Circulation 24 1356, 1961
38 E erts-Suarez, F A., and Carson, C. P The triad of congenital absence of aortic arch (isthmus aortae) patent ductus arteriosus and ventricular septal defect—A trilogy Ann. Surg. 150 153 1959
39 Lev I Pathologic anatomy and interrelationship of hypoplasia of the aortic tract complexes, Lab Invest. 1:61 1952.
40. Noonan, J A., and Nadas, A S. The hypoplastic left heart syndrome Pediat. Clin. North America 5 1029 1958
41 Dorney E. R., Fowler N O and Mannix, E. P Unilateral cl bbing of the fingers due to bsence of aortic arch, Am. J Med 18 150 1955.
42. Merrill, D L., Webster C. A. nd Samson, P C. Congenital absence of the ortic isthmus, J Thoracic Surg 33:311 1957
43 Quie, P G., Novick, R., Adams, P Jr Anderson, R. C., and Vargo, R L. Congenital interruption of the aortic arch, J Pediat 54:87 1959
44. Castellanos, A Garcia, O and Gonzalez, E. Complete interruption of the aortic arch with transposition of the great vessels, Cardiologia 34:33 1959
45 R iz V llalobos, M C DeBalderrama, D P Lopez, J L. V and Castellanos, M Complete interruption of the aorta, Am J Cardiol 8:664 1961

Cardiovascular radiology in acute and chronic Chagas' myocardiopathy

Morphologic and dynamic study of the cardiac contour correlated with the histologic changes observed in myocardiopathies attributed to Schizotrypanum cruzi

*Alfonso Anselmi, M.D.**
*Folga Pisani, M.D.***
*José Angel Suárez, M.D.****
*Orlando Gurdiel, M.D.**
*León Lapco, M.D.**
Caracas, Venezuela

Contradictory and confusing information is found in the available literature on the morphology of the cardiac silhouette seen in acute and chronic Chagas myocardiopathies. Thus, one group of workers[1] attributes the increase in the cardiac shadow to a predominant enlargement of the left ventricle (LV), whereas others[10-13] maintain that, in Chagas myocarditis, cardiomegaly is mostly the result of involvement of the right ventricle (RV).

Radiologic analysis of the cardiac contour in Chagas myocarditis has been limited to the study of the morphology and measurements of the cardiac arches (segments) without any consideration of the changes in position to which the heart is subjected, which are secondary to the enlargement and dilatation of the different cardiac chambers.

Rosenbaum and associates[16] in 1955 and Pifano[12,13] in 1959 and 1960 pointed out that there is a diminution in the visible pulsations of the ventricles in acute and chronic Chagas disease.

It is the purpose of this study to analyze the progressive changes seen in the cardiac contour in acute and chronic Chagas disease in relation to the variations in the position of the heart shown by the electrocardiogram. The different ventricular arches are studied and correlated with the precordial electrocardiographic tracings for the purpose of defining the projection of the ventricles to the external surface of the chest. The morphologic and dynamic

Supported by a grant from the "Fundación José María Vargas," Caracas, Venezuela.
Received for publication July 3, 1966.

*From the Laboratorio de Cardiología Experimental, Instituto de Medicina Tropical, Universidad Central de Venezuela, Caracas, Venezuela.
**From the Departamento de Cardiología, Hospital Universitario, Universidad Central de Venezuela, Caracas, Venezuela.
***From the Instituto de Anatomía Patológica, Universidad Central de Venezuela, Caracas, Venezuela.
Address correspondence to: Dr. Alfonso Anselmi, Laboratorio de Cardiología Experimental, Instituto de Medicina Tropical, Box [illegible], Caracas, Venezuela.

changes shown by the cardiac shadow are correlated with the histopathologic changes.

Materials and methods

Twenty-six patients with the clinical diagnosis of Chagas' myocarditis were selected for this study. Eight of them were studied during the acute stage of the disease (5 males and 3 females). Their ages ranged between 6 and 29 years. In 2 of them the picture at the time of death was that of protracted irreversible cardiac failure. Postmortem studies showed an acute inflammatory myocardial lesion. The leishmanial form of *Schizotrypanum cruzi* was identified in the interior of the myocardial fibers. In all of the acute cases, parasites were found in the peripheral blood.

From a group of 53 patients in whom there was a necropsy diagnosis of chronic Chagas' myocarditis, 18 were selected for this study on the basis of a positive complement fixation reaction (CFR) during life. Pathologic changes were found in the myocardium which were considered to be consistent with the diagnosis of chronic myocarditis. The ages of these patients at the time of death were between 5 and 30 years. Thirteen were males, and 5 were females.

The changes observed in the cardiac shadow in both radiologic and kymographic studies were correlated with the anatomic and histologic changes seen in the heart. In view of the fact that inflammatory processes in the heart cause obliteration of the normal outline of the individual cardiac chambers and of the interventricular groove, electrocardiographic recordings were taken at different levels of the anterior and lateral surfaces of the left hemithorax in order to define the projection of the dilated ventricles on the chest wall. With this approach the identification of each ventricle in the cardiac shadow was easily obtained regardless of the rotation of the heart produced by dilatation of the ventricular chambers.

Results

Acute Chagas' myocarditis. Radiologic studies showed a large massive cardiomegaly in all cases of acute Chagas' disease. Pulsation of the cardiac shadow was invariably decreased. Of interest was the difference between the size of the heart at autopsy and that seen by x-ray study. In the x-ray films the cardiac shadow would seem to be larger than that actually found post mortem.

Pericardial aspiration was attempted in 5 patients, but no fluid was obtained. Two of the patients died in severe heart failure, and the postmortem study disclosed very large flaccid hearts which collapsed and became deformed when they were placed on a flat surface. The ventricular walls were so flabby as to form folds. Cardiac dilatation was chiefly due to enlargement of the right ventricle and the atria.

Microscopic study showed numerous myocardial fibers with intracellular leishmanial forms of *S. cruzi* (Fig. 1,*B*). There were also inflammatory infiltrates of plasmocytes, lymphocytes, and histiocytes scattered all over the myocardium (Fig. 1,*A*). They formed dense focal aggregates of varying size with dissociation of the myocardial fibers (Fig. 1,*C*) which appeared to be fragmented (Fig. 1,*D*). The interstitial space was increased in proportion to the intensity of the inflammatory infiltrate and edema (Fig. 1,*A*, *D*).

The x-ray study of a 10-year-old girl with the clinical picture of acute myocarditis is shown in Fig. 2. Parasites of *S. cruzi* were identified in the peripheral blood. The first study (Jan. 13, 1962) showed a gigantic cardiomegaly with dilatation of all cardiac chambers. No fluid was obtained during an attempt at pericardial aspiration. In the posterior-anterior view (PA), the right inferior arch was very prominent, an evidence of dilatation of the right atrium. The left inferior arch was also prominent. The normal indentations of the cardiac contour had disappeared. In the left lateral projection the right ventricle came in contact with the chest wall, and the left ventricle overlapped the spine. The dilated left atrium displaced the left bronchus. The interventricular groove was not evident, so that the size of each ventricle could not be discerned. Clinically, there were signs of cardiac failure.

Fig. 3 is the electrocardiogram of the same patient as in Fig. 2, taken on th

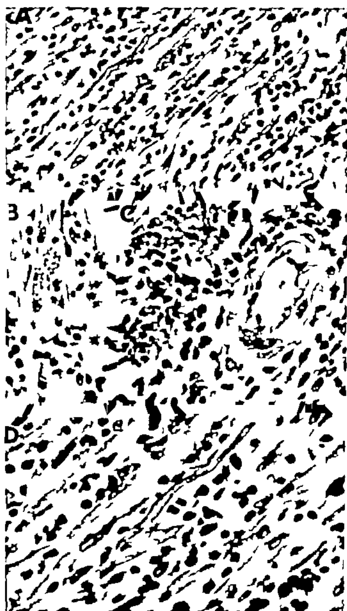


Fig 1 Histopathologic findings in the heart of 17 year-old young man who died with the clinical picture of acute Chagas myocarditis. A Edema and inflammatory cellular infiltrates enlarge the interstitial space between the muscle fibers. *B* A nest of leishmanial forms of *Schizotrypanum cruzi*. *C* Transverse section of blood vessel with normal lumen. Severe scattered inflammatory infiltrates. *D* Atrophic muscle fibers in the midst of inflammatory infiltrate

same date as the x ray films. This tracing showed a first-degree atrioventricular block. There are low voltage of QRS in all leads and a disorder of ventricular repolarization of the extensive subepicardial ischemic type over the anterior and posterior walls of the heart. These signs are indicative of an inflammatory process in the myocardium[13,14]. There are complexes of the Rs and qR type from Lead V to Lead V, indicating that the predominant patterns over the anterior surface of the chest arose from the left ventricle and suggesting that the main component of cardiomegaly in the LA view in the radiologic study could be attributed to the left ventricle.

Twenty days later the cardiac shadow



Fig 2 Cardiovascular contour the PA and left lateral view in 10-year-old girl with acute Chagas myocarditis. All cardiac cavities are dilated. The normal outlines of the cardiac chambers and the interventricular groove has disappeared.

was noticeably reduced in size (Fig 4). In the PA view the right and left inferior arches are smaller. The indentations of the cardiac shadow and the interventricular groove are still not visible. The kymographic study shows that the cardiac pulsations were markedly decreased both in systole and diastole. At the level of the right inferior and left inferior arches there is a marked diminution in the visible pulsations of both ventricles. In the electrocardiogram the A-V block has disappeared and the voltage of QRS has increased in all leads. These findings probably indicate that the myocardial inflammatory process had decreased. The presence of Rs and qR complexes from Lead V to Lead V indicates that the left ventricle was projected on these areas, suggesting that the left inferior arch of the PA view was produced by it.

Figs. 5 and 6 are from the same patient $1\frac{1}{2}$ months after the previous observation. In the PA view the cardiac shadow is within normal limits whereas the electrocardiogram shows an increase in voltage of QRS and a certain degree of flattening of the T wave in Leads V to V.

In the PA view the kymogram shows decreased pulsation of the left inferior arch. In the left oblique view the pulsation of the right inferior arch becomes normal. At the left inferior arch the pulsation remains diminished. It is at the left inferior arch in the PA projection that the changes in ventricular motion are seen. This arch is formed by the left ventricle at which level the electrocardiographic changes of subepicardial ischemia were found.

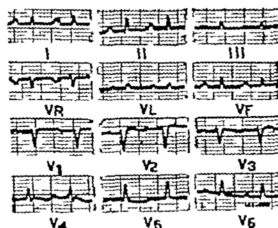


Fig 3 Electrocardiogram of the same patient. Fig 3 Sinus rhythm 146 per min. P-R 0.20 sec. $\hat{A}_{QRS}$ +60 low voltage of QRS all leads. The T waves flat in all leads.

Chronic Chagas myocarditis. Radiologic studies showed considerable cardiomegaly (Grade III to IV) in 15 of the 18 patients with chronic Chagas myocarditis. In

Fig. 4. Radiologic, kymographic, and electrocardiographic modifications in the same patient as in Fig. 2. There is a decrease in the cardiac contour while the outline of the cardiac chambers remains effaced. The kymogram shows a marked decrease in pulsatility of both ventricles. The A-V block is no longer present in the electrocardiogram and the voltage of QRS has increased in every lead.

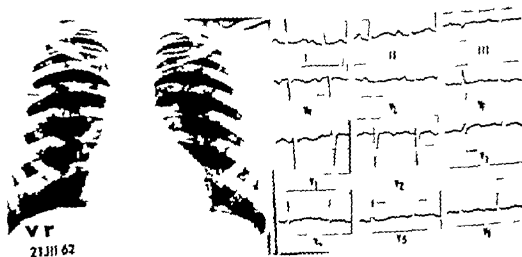


Fig. 5. Same patient as in Fig. 4, 68 days after the first study. The heart shadow has become normal and the electrocardiogram shows flattening of the T waves in Leads V[illegible] and V4.

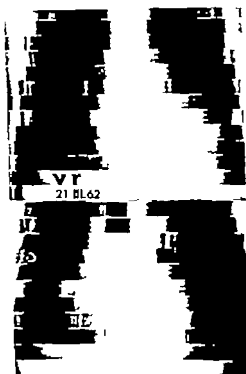


Fig 6 Kymographic study of the same patient as in Fig 5 in the P\ view There is marked decrease in systolic and diastolic pulsations at the level of the left inferior arch. I the left anterior oblique iew marked decrease in the left inferior arch is seen, whereas in the right anterior oblique view the cardiac pulsation is normal.

every one of these the cardiac pulsations were markedly decreased in both ventricular cavities. In 2 patients there was evidence of a moderate enlargement of the heart (Grade II cardiomegaly) whereas the amplitude of the cardiac pulsations was either normal or slightly increased In one pat ent the size of the heart and the cardiac pulsations were normal.

Fig 7 shows the x-ray studies and the electrocardiogram in a 29-year-old patient with a positive epidemio ogic history of *S cruzi* infection and positive CFR to *S cruzi* The cardiac shadow is normal and the electrocardiogram shows complete right bundle branch block, with frequent multifocal extrasystolic beats. The histopathologic study of the heart showed a diffuse inflammatory infiltration irregularly distributed throughout the wall of the ventricles and the interventriculα septum. There was diffuse moderate fibrosis, which in some areas of the ventricular walls was condensed forming irregular plates of fibrotic tissue with some myocardial fibers in their midst showing severe degenerative changes.

Fig 8 shows the x ray film and electrocardiogram of a 21 year-old male patient who had a clinical picture of advanced chronic Chagas myocarditis. In the PA view the cardiac shadow is enlarged with dilatation of all cardiac chambers. The indentations of the silhouette have disappeared In the left oblique projection (Fig 9) dilatation of both ventricles is apparent and the interventricular groove cannot be recognized The right anterior oblique view shows displacement of the barium filled esophagus by a dilated left atrium The electrocardiogram taken on the same day as the radiologic picture shows a first-degree A V block enlargement of both atria and ventricles, and incomplete left bundle branch block An rS type of ventricular complex was recorded in Lead V_1 The QS complexes which were obtained from Lead V to Lead V indicate the presence of an electrically inactive area involving the anteroseptal surface of the heart. These changes suggest that the heart has a clockwise rotation around its longitudinal axis, whereas the right ventricle is projected onto the anterior portion of the chest from Lead V to Lead V_5. The left ventricle is projected toward the level of the middle axillary line (V_6) The electrical position of the heart indicates also that the left inferior arch of the radiologic projection in the PA view corresponds to the right ventricle.

The pulsations of the left inferior arch of the cardiac silhouette were markedly decreased and almost absent in ts middle portion as shown by the PA kymographic study made at this time (Fig 10) The left oblique position revealed a d minished amplitude of the cardiac pulsations in both the left and the right lower arches Even though the pulsations were decreased in both ventricles the finding was more pronounced for the right ventricle.

The postmortem study of this case showed a globular-shaped heart (Fig 11)

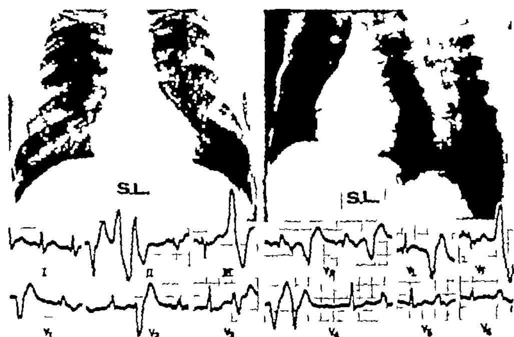


Fig. 7. I ... ar-old patient with chronic Chagas myocarditis. The heart shadow is normal in the PA and left ... The electrocardiogram shows right bundle branch block. Ventric... tation ... sed.



Fig. 8. Heart shadow and electrocardiogram of a 21 year-old male patient with chronic Chagas myocarditis. In the PA view the size of the heart is increased. The normal indentations of the cardiac silhouette have disappeared. The electrocardiogram shows that the atria and both ventricles are enlarged. There is a ... rotation of the heart on its longitudinal axis. Incomplete left bundle branch block is present. There is an electrically inactive zone over the anteroseptal aspect of the heart.



Fig 9 Left terior and right anterior oblique iews of the same patient as in Fig 8 There is dilatation of both ventricles and disappearance of the interventricular groov The esophagus has been displaced by the left trium.

that weighed 600 grams. The walls were flabby and the heart became flat and formed folds when it was placed on a hori zontal surface. All of the heart chambers were dilated (Fig 11) There was extensive thrombosis in the apex of the right ven tricle and also to a lesser degree in the left ventricle. The A V valvular rings were dilated The wall of the left ventricle was 14 mm. thick at the base and the anterior and lateral walls were 7 mm thick The thickness of the wall of the right ventricle was 3 mm at the base and 2 mm at the level of the trabecular zone. Microscopic examination revealed large confluent scars (Fig 12) forming irregular plaques of fibrotic tissue. Intermingled with these plaques were numerous myocardial fibers that exh bited different degrees of degenera tive changes. The fibrotic plaques were particularly numerous in the trabecular zone of the right ventricle. In this area they involved the entire thickness of the wall and resembled the scar tissue usually found after myocardial nfarction No vascular lesions were found and the coronary arteries were patent. The endocar d um which was rough and fibrotic over the trabecular zone, showed extensive thromboses as seen in Fig 11 A dense lympho-histiocytic infiltrate scattered n multiple foci was present. In the apex of the left ventricle the wall had been re

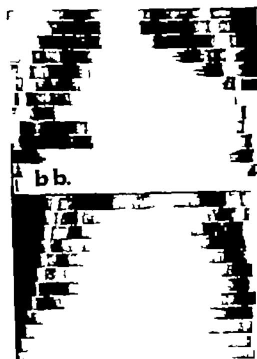


Fig 10 Same patient as in Fig 8 K mographic study done on the same day as the previous radiologic studies (Fig 9) showing decreased amplitude of the cardiac pulsations the PA iew along the left nferior arch the middle portion of this arch show almost no motion I the left anterior oblique iew pulsations are decreased t the level of both the righ nd the left entricles The righ entricle shows smaller pulsations.

placed by fibrous tissue. The few remaining myocardial fibers showed variable degrees of degeneration and there was also a sparse inflammatory infiltrate (Fig. 12).

Discussion

An analysis of the results shows that there is a definite relationship between the changes in the cardiac shadow and the motion of the free ventricular walls with respect to the histologic changes which the *Schizotrypanum cruzi* causes in the myocardium. Following Chagas' classification[19] the results observed during the acute and the chronic stages of the disease will be analyzed separately.

Acute Chagas' myocarditis. Acute Chagas' myocarditis is characterized histologically by the presence of numerous leishmanial forms of *S. Cruzi* in the interior of the myocardial muscle fibers, mononuclear infiltrate, and inflammatory edema.[11, 8-43] Cross and associates[32] showed experimentally that the ventricular diastolic pressure increases in proportion to the degree of myocardial edema, beginning when the latter comprises 4 to 5 per cent of the original weight of the heart.

The increased ventricular diastolic pressure in turn acts upon the wall of the ventricle, whose muscle fibers are dissociated by the infiltrate and the inflammatory edema. This leads to an increase in the volume of the heart which causes the cardiac shadow (as seen on x-ray films) to become enlarged, and which appears to be greater than that found post mortem.

In acute Chagas' myocarditis the heart shows morphologic changes that are dependent upon the intensity of the inflammatory process. If the cellular infiltrate and the interstitial edema are slight and distributed only in scattered areas, the increase in diastolic pressure and the interstitial changes will be minimal and the size of the heart will hardly be altered. If the infiltrate and the edema are considerably augmented, the rise in diastolic pressure will be greater, and will considerably increase the volume of the heart. Between these two extremes there may be a whole spectrum of cardiac sizes, as reported by Laranja and associates.[16] Morphologically it would be difficult to attribute a given configuration of the cardiac shadow to acute Chagas' myocarditis. The cardiomegaly in acute Chagas' myocarditis has been attributed to right ventricular enlargement[33] and to left ventricular enlargement.[4, 8, 34] Experimental studies[11] and clinicopathologic observations[[illegible]] reveal that the inflammatory process produced by *S. cruzi* in the myocardium does not follow a definite systematization but rather a random distribution involving one ventricle or the other. It would seem to be reasonable that the predominance of the enlargement of one chamber or another depends on the degree of inflammatory process at the particular level involved.

Johnson[32] has pointed out that the initial measure and the amplitude of the contraction of the muscle fibers are of great importance in the regulation of intramyocardial pressure. Cross and associates[32] and Salisbury and associates[41] proved that myocardial edema and injury of heart muscle cause a reduction in the distensibility of the myocardial fiber. Muscle fibers with pathologic changes are frequently found in the midst of the foci of cellular infiltrates in Chagas' myocarditis. The fundamental cause of degeneration of the fibers is anoxia resulting from vascular factors[[illegible]] or from disorders of oxygen diffusion.[11, 34] Both factors which determine a marked reduction in the distensibility of the myocardial fibers are present in acute Chagas' myocarditis. The reduced distensibility of the myocardial fiber causes the initial length of the fiber during systole to be less than normal, which in turn leads to decreased contractile force. This is expressed dynamically by decreased pulsations of the heart during systole and diastole.

Chronic Chagas' myocarditis. Histologically chronic Chagas' myocarditis is characterized by the presence of degenerative processes in the myocardial fibers, as well as by proliferation of fibroblasts with the formation of small fibrotic plaques distributed throughout the entire myocardium.

In cases of chronic myocarditis due to *S. cruzi* shown in other series there was a close relationship between the intensity of the histologic changes and the increase





Fig 11

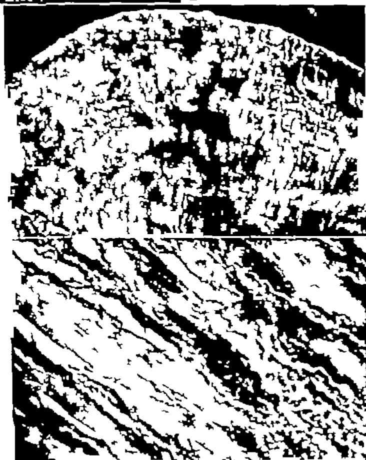
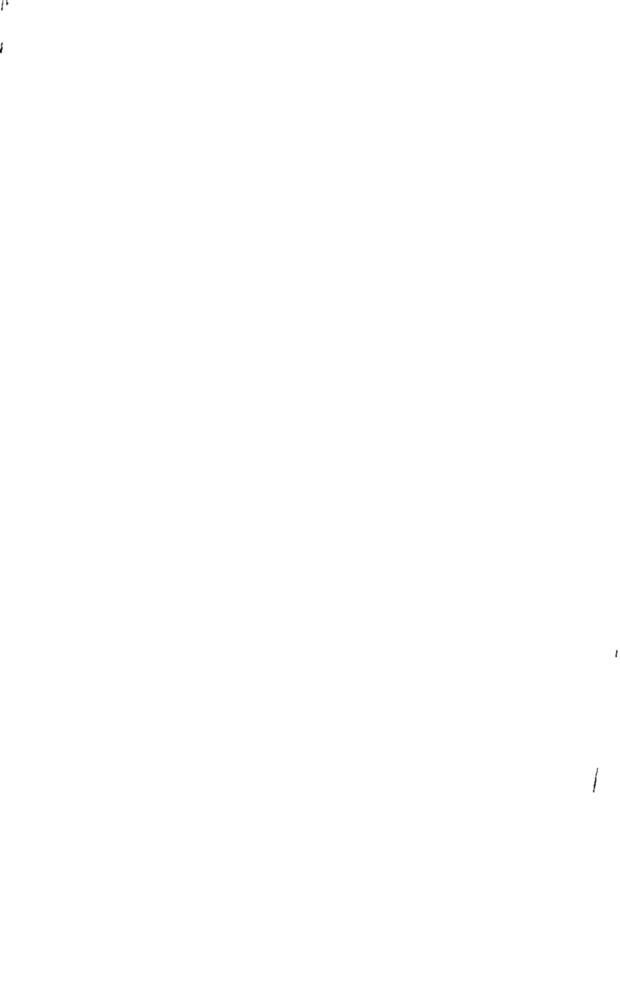


Fig 12

Fig 11 Same patient as in Fig 8. The heart weighed 600 gr ms The specimen is seen from he righ and left hambers At the apex of the left ventricle there is aneurysm tha measures 1 5 cm in diameter ith intra mural thrombi.

Fig 12 Microscopic study of the same patient as in Fig 11 *Above* My ardium with multiple scar of arious sizes and shapes sca tered diffusely *Below* Proliferation of the interstitial connecti tissue in which he collagen fibers (in red) are forming bundant bands The musc o be fragmented. (V Gieson ×460)



in the volume of the heart.[15,17,18,25] The conclusion based on these facts is that the size of the cardiac shadow in chronic Chagas myocarditis will depend upon the degree of myocardial lesions as well as upon the location of these lesions. The size of the heart may vary from nearly normal to enormously hypertrophied.

In order to compensate for the functional deficiency of the destroyed myocardial fibers and to maintain circulatory dynamics dilatation of the ventricular chambers takes place. Ventricular dilatation was greater where the fibrotic areas were more extensive and marked. Because the contractile force of the muscle fiber depends upon the initial resting distention[28] the ventricular dilatation observed in this disease accounts for the motion of the heart.

The compensatory mechanisms in the dynamic pressure-volume curves of the dog heart in response to an increase in inflow pressure have been shown experimentally by Rosenblueth and associates.[27,28] In cases of cardiac dilatation due to chronic Chagas myocarditis, the ventricular pulsations are either normal or increased. By analyzing the work of a muscle fiber as a function of its initial length, Doi[29] found that the maximal work increased with an increase in the initial length of the muscle fiber. However when the initial length of the muscle fiber at rest goes beyond certain limits, the maximal work developed by the fiber diminishes; these facts explain the decrease in contractile force of the heart seen in huge cardiac dilatations in advanced chronic Chagas myocarditis. This advanced stage of the disease was always associated with irreversible heart failure.

It should be pointed out that, in one of the acute cases described here (Figs. 5 and 6) the dynamics of the left ventricular arch remained decreased in amplitude despite the fact that the cardiomegaly had disappeared and the shape and size of the heart had become normal. This unusual finding is to be explained on the basis of fibrous sequelae consequent to the acute inflammatory process and is not due to the mechanisms invoked above in those cases with huge cardiac dilatation during the chronic stage of the advanced forms of the disease.

In this series there was a decrease in cardiac pulsatility both during systole and diastole and more pronounced on the left inferior arch in the PA view. According to the electrocardiographic patterns obtained in the left chest, this arch may correspond either to the left or to the right ventricle.

Summary

The cases of 26 patients with Chagas myocarditis have been analyzed with regard to the relationship between the x ray changes, stage of the disease, and pathologic changes. Eight of these patients were seen during the acute stage of the disease and 18 during the chronic stage. All of the patients with the acute form of the disease had *Schizotrypanum cruzi* in the peripheral blood. Two patients died. Nests of Leishmania within the myocardial fibers were found at autopsy.

From a series of 53 autopsies of patients with chronic Chagas myocarditis and a positive complement fixation reaction to *Schizotrypanum cruzi* 18 cases were selected for study (all of these patients were under 30 years of age). They showed histologic changes of varying degree consistent with a diagnosis of chronic myocarditis.

The morphologic and dynamic data of the cardiac contour were analyzed and the electrocardiogram provided an accurate outline of the projection of each ventricle onto the chest wall.

The pathologic findings were correlated with the radiologic and kymographic findings. In acute Chagas myocarditis the increased size of the cardiac shadow and the decreased amplitude of the cardiac pulsations are related to the severity of the inflammatory process. The altered morphology and cardiac dynamics seem to be related to the cellular infiltrate and the inflammatory edema of the myocardium.

In chronic Chagas myocarditis there is a close relationship between the intensity of the myocardial fibrosis, cardiac enlargement, and the decreased motility of the heart. The increase in the length of the myocardial fibers and the myocardial

fibrosis are seemingly responsible for these findings

We are indebted to Dr Alberto Rivero of the Instituto de Anatomía Patológica, Universidad Central de Venezuela for his extensive collaboration

REFERENCES

1 Alvarez, J and Carvajal, V Tripanosomiasis cardiaca americana. Investigación clínica y electrocardiográfica Comunicación preliminar Rev Méd Chile 69:833 1941
2 Cossio, F Estudio actual de nuestros conocimientos sobre la miocarditis chagásica, Rev Med. Tucumá 11 1943
3 Alvarez, A J and Rosenbaum, M B Radiología cardiovascular en la miocarditis crónica chagásica Rev Argent Cardiol 20 146, 1953
4 Freitas, J L P Lion M F and Tartari, J T Resultados de um investigação sobre moléstia de Chagas realizada no Município de Marília outros, com estudo clínico de dois casos agudos da doença, Rev Hosp Clin. Fac Medic S P 1 8:81 1933
5 Mivar S and Vidaler L A L caso de miocarditis chagásica aguda evolutiva con grave insuficiencia cardiaca, Día Méd 26:349 1954
6 Mon, B Miocarditis crónica chagásica (Trypanosomiasis americana) Día Méd. 27:983 1955
7 Rosenbaum M B and Alvarez, A J The electrocardiogram in chronic chagasic myocarditis Am Heart J 50:492 1955
8 Isasi, E J and Correa Durán, A Miocarditis chagásica crónica, Arch Urug Méd Cirug y Espec 19 186 1956
9 Franco de Oliveira, P Formas clínico-evolutivas da cardiopatia chagásica crônica. Tese de concurso docencia livre da cadeira de línica propedeutica medica da Faculdade de Medicina de Universidade de Paraná Curitiba, 1958.
10 Rosenbaum, M B., Hojman, D and Del Zar L E. Pericarditis serohemorrágica en la miocarditis crónica chagásica, Rev Argent Cardiol. 22:178, 1955.
11 Montoreano, F and Rabenko, J El problema diagnóstico de la cardiopatía chagásica en pacientes de edad avanzada, Prensa Méd. Argent. 43:2490, 1956.
12 Pifano, F Algunos aspectos de la enfermedad de Chagas en Venezuela. Primer Congreso Internacional sobre Enfermedad de Chagas, Oficina Gráfica da Universidade do Brasil 1:89 1959
13. Pifano, F Algunos aspectos de la enfermedad de Chagas en Venezuela, Gac. Méd. Caracas 68 1 1960.
14 Walerach, S., Perdomo, R., Dighiero, J Osimani, J J Franca, M E., and Folle J A. Miocarditis chagásica crónica (dos nuevos casos en el Uruguay) Torax 3:215 1954
15 Pifano, F Anselmi, A., Alemán, C., Suárez, J A., and Díaz Vázquez, A. Miocardiopatía chagásica experimental. Valoración del método de investigación experimental para el estudio de las propiedades fundamentales del corazón del perro con infección chagásica aguda y crónica, Arch Venez. Med. Trop. 4:37 1962.
16. Laranja, F Dias, E., Nobrega, G., and Miranda, A Chagas disease. A clinical, epidemiologic and pathologic study Circulation 14 1035 1956.
17 Gore, I and Saphir O Myocarditis. A classification of 1 402 cases, Am. Heart J 34:827 1947
18. Chagas, C. Trypanosomiase americana. Forma aguda da moléstia, Mem. Inst. Oswaldo Cruz. 8:37 1916.
19 Vianna, G Contribuição para o estudo da anatomia patológica da moléstia de Chagas (Esquizotripanose humana ou tireoidite parasitária) Mem Inst. Oswaldo Cruz 3:276, 1911.
20. Torres, M Estudo do miocárdio na moléstia de Chagas (forma aguda) Alterações da fibra muscular cardíaca, Mem. Inst. Oswaldo Cruz 9 114 1917
21 Torres, M and Tavares, B M Miocardite no macao Cebus pos inoculações repetidas com Schizotrypanum cruzi, Mem Inst. Oswaldo Cruz 56:85 1958
22 Cross, C. E. Rieben, P A., and Salisbury P F Influence of coronary perfusion and myocardial edema on pressure-volume diagram of left ventricle Am. J Physiol. 201 102, 1961
23. Mazza, S Sabate, E and Arigu M Observaciones de formas agudas de enfermedad de Chagas originarias de Tucuman y Salta, Arch. Oftalmol Buenos Aires 14:504 1939
24 González, G and Rivarola, J B Enfermedad de Chagas aguda. Primer caso autóctono identificado el Paraguay An. Fac. Cienc. Med. 7:39 1939
25 Tejada, V C., and Castro, F Miocarditis crónica en Guatemala, Rev Col. Méd. de Guatemala, 9:63, 1958.
26 Dias, E Laranja, F S. and Nobrega, G. Doença de Chagas, Mem. Inst. Oswaldo Cruz. 43:945 1945
27 Décourt, L V Romeiro Neto, M and Freitas, J L P Alterações cardíacas na moléstia de Chagas O Hospital 29:286, 1946.
28. Romaña, C. Miocarditis crónica esquizotripanósica, An. Inst. Med. Regional 2 1 1947
29 Laranja, F S., Dias, E., Duarte, E., and Pellegrino, J Observações clínicas epidemiológicas sobre a moléstia de Chagas no Oeste de Minas Gerais, O Hospital 40 137 1951
30. Andrade, Z. A., and Andrade, S. G A patologia da doença de Chagas (forma crônica cardíaca), Bol. Fund. Gonçalo Moniz. 6 1 1955
31 Walerach, S. Fabius, A., Cirilo, J P and Acosta Ferreira, W; Infarto de miocardio en la cardiopatía chagásica Tórax 4:255, 1955.
32. Torres, M Anatomia patológica de cardiopatia crônica chagásica, Rev Goiana Med. 5 177 1959
33 Johnson, J R. Factors controlling intramyocardial pressure Fed. Proc. 4:37 1945
34 Salisbury P F., Cross, C. E., and Rieben, P A.; Distensibility and water contents of

heart muscle before and after injury. Circulation Res. 8:788, 1960.

35. Torres, M.: Miocitolise fibrose do miocárdio na doença de Chagas, Mem. Inst. Oswaldo Cruz 58:161, 1960.

36. Anselmi, A., Pifano, C., F., Suárez, J. A., Domínguez, A., Díaz Vázquez, A., and Anselmi, G.: Experimental Schizotrypanum cruzi myocarditis. Correlation between histopathologic and electrocardiographic findings in experimental Chagas heart disease, Am. Heart J. 70:638, 1965.

37. Rosenblueth, A., Alanís, J., and Rubio, R.: Some properties of the mammalian ventricular muscle, Arch. Int. Physiol. 67:276, 1959.

38. Rosenblueth, A., Alanís, J., López, E., and Rubio, R.: The adaptation of ventricular muscle to different circulatory conditions, Arch. Int. Physiol. 67:358, 1959.

39. Doi, Y.: Studies on muscular contraction. II. The relation between the maximal work and the tension developed in muscle twitch, and the effects of temperature and extension, J. Physiol. 54:335, 1921.

Experimental and laboratory reports

The orthogonal electrocardiogram as an index of digitalis response in normal adults

*James R. Snyder, M.D.**
Hubert V. Pipberger, M.D.
Washington, D.C.

A useful quantitative index of digitalis response in man has not been demonstrated despite numerous studies.[1] The slowing of the ventricular rate after digitalis in patients with congestive heart failure who are in atrial fibrillation is a notable exception.

Several factors contribute to make this a difficult area to study. First, the ECG changes after digitalis occur mainly in the ST-T portion and resemble the nonspecific ST-T changes which may result from a multitude of causes. Second, prior to the use of corrected orthogonal lead systems, quantitative data were usually expressed in descriptive terms and based on observations using conventional lead projections. Third, the ECG effects of digitalis are probably dependent on the state of the myocardium,[2-4] and confusion may result when the responses of inhomogeneous groups are compared.

In the present controlled study using intravenous digoxin, the electrocardiographic response of normal adult subjects was quantitated. It was anticipated that the advantages of using a corrected orthogonal lead system for the acquisition of data, and a digital computer for subsequent analysis would enhance this quantitation and permit a variety of ECG measurements to be examined.

Methods

Twenty studies were done on 12 subjects who ranged in age from 34 to 55 years, with an average of 44 years. All subjects were male hospitalized patients admitted for noncardiovascular problems. The cardiac evaluation was normal in each.

The 8-hour studies commenced at 7:30 A.M. with the subjects fasting and resting in bed. A standardized light lunch was served after the 4-hour recording, and limited ambulation was permitted. Smoking was interdicted. Simultaneous X, Y, and Z leads were recorded on FM magnetic tape using Frank's lead system with the thoracic electrodes at the level of the fourth intercostal space.

After a base-line recording, the subjects received either 1.6 mg. of digoxin intravenously (10 subjects, digitalis group) or an equal volume (6.4 c.c.) of normal saline

From the Veterans Administration Research Center for Cardiovascular Data Processing, and the Department of Medicine, Georgetown University School of Medicine.
Supported in part by United States Public Health Service Research Grants from the National Heart Institute, No. HE 09686-05, and the Division of Chronic Diseases, No. CD 00064-06.
Received for publication June 13, 1966.
*Work performed during tenure of a United States Public Health Service Fellowship from the National Heart Institute, No. HE 29 843-05.
Address correspondence to: Dr. James R. Snyder, Division of Cardiology, Doctors Hospital, 1815 I St., N.W., Washington, D.C., 20006.

(10 subjects, control or placebo group). Eight subjects were common to both groups having undergone a control study at some time prior to receiving digitalis. The intravenous injection was given over a 3-minute period and the temporal sequence started at the midpoint of injection. Orthogonal electrocardiograms were taken at 5, 10, and 30 minutes, and at 1, 2, 4, 6, and 8 hours. Daily recordings were obtained in the digitalis group over an additional 4 days. These tracings were taken in the morning with the patient fasting and in a resting supine position.

In preparation for analysis the X, Y, and Z leads were each digitized at a sampling rate of 1,000 per second. An IBM 7094 digital computer was used for further processing and analysis of data. Details of the computational process have been reported. Two hundred different ECG measurements were examined including P, QRS, and ST-T wave durations with magnitude and direction of their maximal and instantaneous vectors. Time integral measurements were determined by electronically computing the algebraic sum of the areas enclosed by the respective wave forms. Time integrals for the QRS included the P wave. Because of the inability to define the beginning of the T wave, the term "ST-T complex" is used for that time integral measurement. The X, Y, and Z components were added vectorially to obtain spatial vectors.

The Q-T interval was corrected for heart rate.[3]

Results

After intravenous digoxin there was a consistent change in the ST-T complex from base-line recordings, and an obvious difference from control subjects was readily apparent. The two ECG measurements which best expressed these changes were the spatial magnitude of the maximal T vector and the spatial magnitude of the time integral of the ST-T complex. The Q-T index also decreased in all subjects after digitalis but the magnitude of change when compared to that of the control group was not sufficient to permit its use as an index of the digitalis response (Tables I and II).

Within 30 minutes after digoxin was injected the spatial magnitude of the maximal T vector had decreased an average of 37 per cent from the base-line recordings in the digitalis group. There was nearly a 50 per cent decrease in 2 hours. The maximum response was reached in 4 to 6 hours, by which time it had decreased 60 per cent from pre-digitalis levels (Fig. 1). This marked response provided a complete separation between the digitalis and control groups which was

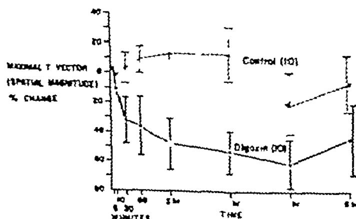


Fig. 1. The temporal response of the subjects receiving digitalis is well described by changes in the spatial magnitude of the maximal T vector expressed as per cent deviation from base-line values. Vertical bars represent ± 1 standard deviation. Note the nonspecific T-wave change in the control group at 6 hours. When the response of individual subjects was plotted, there was complete separation between the two groups beginning at 30 minutes and continuing through the 4-hour recording.

Table I. Effect of intravenous digoxin on ECG measurements in digitalis and control groups of 10 subjects each (mean data)

	Hours after injection						
	0	½	1	2	4	6	8
Spatial magnitude (mv) of maximal T vector							
Control	42 (13)	43 (14)	45 (15)	47 (16)	46 (11)	34 (19)	42 (16)
Digitalis	42 (16)	30 (16)	28 (16)	25 (15)	20 (11)	18 (11)	23 (13)
Spatial magnitude of S ĀT (μv sec.)							
Control	54.4 (20.7)	55.2 (15.8)	58.1 (16.4)	59.1 (18.1)	55.5 (17.9)	42.0 (20.5)	49.4 (17.7)
Digitalis	51.3 (20.4)	32.4 (18.7)	32.5 (17.5)	23.8 (16.1)	20.8 (11.9)	21.4 (11.5)	25.7 (11.5)
Azimuth of S ĀT (degrees)							
Control	45 (18)	44 (18)	45 (17)	41 (15)	40 (19)	59 (20)	49 (20)
Digitalis	55 (21)	52 (21)	54 (27)	60 (24)	77 (44)	102 (58)	76 (35)
Elevation of S ĀT (degrees)							
Control	11 (12)	11 (10)	15 (12)	15 (14)	16 (12)	3 (23)	13 (17)
Digitalis	13 (15)	4 (27)	−4 (33)	−4 (33)	−19 (25)	−27 (29)	5 (25)
Heart rate							
Control	67 (8)	66 (6)	67 (8)	65 (10)	63 (8)	71 (11)	73 (10)
Digitalis	68 (11)	56 (6)	54 (6)	57 (9)	58 (8)	75 (14)	68 (13)
Q-T index (msec.)							
Control	404 (23)	412 (23)	403 (11)	407 (25)	403 (19)	392 (31)	407 (29)
Digitalis	407 (22)	373 (26)	360 (23)	357 (34)	356 (28)	382 (33)	379 (34)
P-R interval (msec.)							
Control	157 (17)	158 (16)	161 (21)	162 (18)	161 (26)	158 (21)	158 (32)
Digitalis	158 (20)	174 (30)	172 (28)	177 (34)	184 (89)	178 (49)	168 (35)

Mean ECG changes during an 8-hour period after intravenous injection of mg. of digoxin or of normal saline. A significant response in the subjects receiving digitalis, when compared to the control group (< 0.005) was observed at some time in each of the measurements except the P-R interval. Changes in the Q-T index and the T-wave amplitude appear to provide the most significant response to digitalis, when the absolute values are compared. Table II expresses these changes as the per cent change from base-line values. Note the control (placebo) group response at 4 hours.

Figures in parentheses represent ± 1 standard deviation. Figures underlined represent significance level of < .005 from the respective control group.

*Table II. Mean ECG response of digitalis and control groups of 10 subjects each. Expressed as per cent change (+ or −) from base line**

	Hours after injection						
	0	½	1	2	4	6	8
Spatial magnitude of maximal T vector							
Control	0	+ 3	+ 9	+13	+14	−21	− 6
Digitalis	0	−33	−37	−48	−53	−61	−44
Spatial magnitude of SÂT							
Control	0	+ 5	+12	+12	+ 5	−22	− 6
Digitalis	0	−40	−39	−56	−58	−61	−47
Q-T index							
Control	0	+ 2	0	+ 1	0	− 3	+ 1
Digitalis	0	− 8	−11	−12	−13	− 6	− 8

*Mean changes in the three ECG measurements which best describe the temporal response of the digitalis group (Table I). The variability of the T-wave measurements among normal individuals results in a large range, thereby making statistical evaluation of absolute values apparently less significant (Table I). However, when the data are expressed as the percentage change from base-line values, the significance of the T-wave changes in the digitalis group during the 8-hour study becomes evident.
† Underlined figures represent significant difference ($p < 0.001$) from the mean of the control group.

present at 30 minutes and continued through the 4-hour tracing. Similar changes were noted in the time integral. Other ECG measurements were generally less satisfactory (Table I). A significant statistical separation between the digitalis and control groups was not possible at either 5 or 10 minutes after injection.

The T wave diminished in 9 of the 10 control subjects (placebo group) 6 hours after injection and 2 hours after lunch. At that time the T wave, which had shown little change during the initial 4 hours, decreased 22 per cent from its base-line level. Despite this change, a highly significant separation ($p < 0.001$) of the digitalis group from the control group was possible.

When the T wave variation which occurred in the control group at 6 hours was subtracted from the response of the subjects receiving digitalis, the maximum response occurred at 4 hours. Two thirds of this peak effect was present at 30 minutes and 95 per cent of the maximum at 2 hours. Diminution of the digitalis effect was consistently observed 8 hours after injection, although a measurable effect was still evident 4 days later (Table III).

Changes in the T wave, although primarily of magnitude, were also associated with less obvious directional changes. Four hours after digitalis, 8 of the 10 subjects demonstrated an increased angle of elevation (25 to 50 degrees) of the time integral of the ST-T complex, whereas 4 showed an anterior rotation, increasing the azimuth angle greater than 24 degrees from base-line values. No corresponding change was observed in the control group.

No symptoms of clinical toxicity were noted in the subjects receiving digitalis.

Discussion

The present study, done in an age group in which clinical heart disease is commonly seen, confirms previous data in younger subjects which demonstrated that the spatial magnitude of the time integral of the ST-T complex is a reliable index of the temporal course of digitalis effect in man. The use of corrected orthogonal leads, tape recording equipment, and a digital computer for ECG analysis permitted 300 different ECG measurements to be examined while reducing the redundancy and lead distortion inherent in conventional 12 lead electrocardiogram. The three simultaneous leads also improve

*Table III. Mean ECG response of digitalis and control groups of 10 subjects each. Expressed as per cent change (+ or −) from base line**

	Hours after injection					
	0	*4*	*24*	*48*	*72*	*96*
Spatial magnitude of maximal T vector						
Control	0	+14 (18)	—	—	—	—
Digitalis	0	−53 (14)	−26 (15)	−35 (21)	−30 (18)	−20 (22)
Spatial magnitude of SÂT						
Control	0	+5 (16)	—	—	—	—
Digitalis	0	−58 (20)	−32 (28)	−38 (23)	−37 (18)	−29 (27)

*Mean response of the digitalis group over 4-day period. The data are expressed as per cent deviation from base line, and an effect is still evident 4 days after intravenous digoxin. Control observations on the day-to-day variability of these subjects are not available for comparison.

Figures in parentheses represent ±1 standard deviation.

the accuracy of time base measurements such as the P-R and Q-T intervals.

The ST-T complex apparently contains the most information and the spatial magnitude of the maximal T vector and that of the time integral of the ST-T complex best quantitate the response to digitalis. The spatial magnitude of the maximal T vector, which is simply calculated as the square root of the sum of the squares of the maximal T deflections in each of the three orthogonal leads (X, Y, Z) appears to be the most useful index (Fig. 1). The problems involved in the calculation of the time integral measurement[11] tend to limit its application unless electronic computers are available for analysis. Changes in other ECG items which were anticipated as being useful, such as heart rate, Q-T index, P-R interval, and directional changes in the ST and T wave, were neither consistent nor so significantly altered by digitalis as were the T wave measurements (Tables I and II).

The effect of digitalis on the forces of ventricular repolarization as recorded from skin electrodes can be easily appreciated in either the scalar or loop displays.[14] Computation further provides a more complete record of these temporal changes. The similar shape and parallel course of changes in the temporal response curves of other parameters of cardiac function in man after digoxin are consistent with the present observations.[19] These data suggest that intravenously administered digoxin produces a substantial effect within 30 minutes, and a near peak effect at 2 hours after injection. A diminution in the peak response to digoxin was consistently observed 8 hours after injection, although a measurable effect was present 4 days later.

During the initial 4 hours of the study the subjects remained fasting and resting in bed. During this period the T wave measurements of the control group remained stable after injection of normal saline. However, within 2 hours at the 6-hour tracing, changes in the T wave were apparent. This effect was considered to be due in part to the postprandial state. Several comments may be made concerning this observation. First, the change in the T wave was primarily one of magnitude and was similar to the effect of digitalis. Second, its influence on the 6-hour response in the group receiving digitalis might have been additive, thereby making the 6-hour maximum response more apparent than real. A correction in the temporal response curve of the digitalis group would place the peak response at 4 hours after injection. Third, a significant separation between the digitalis and control groups ($p < 0.001$) was still possible using the spatial magnitude of the maximal T vector.

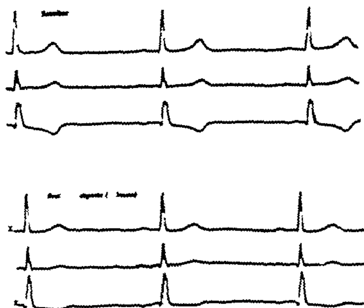


Fig. 2. The three orthogonal leads X, Y, and Z (reversed polarity in Z) are shown before and 6 hours after 1.6 mg. of digoxin intravenously. Observe the change in the size of the T wave, whereas directional changes are not obvious. This series is characteristic of the response to digitalis in these normal subjects. No deviation in the P or QRS observed.

The changes in the ST T wave frequently described in the electrocardiogram secondary to digitalis consist of a sagging S-T segment followed by a predominantly negative T wave. These changes are most commonly observed in the leads demonstrating the largest QRS deflection and describe an orientation of the ST T forces 180 degrees opposite those of the QRS. These gross changes were never observed in this group of normal subjects, despite the relatively large dose of digitalis. It is possible that healthy subjects tolerate digitalis better than does a clinical population and the changes are a matter of degree or perhaps that failing hearts have a qualitatively different ECG response to digitalis as has been suggested. It was of considerable interest therefore that, although a directional change in the T wave was not apparent in the loop and scalar displays 4 hours after digitalis (Fig.) some subjects showed significant changes in the azimuth and elevation angles of the time integral of the ST T complex. No corresponding change was observed in the control group. Thus the directional change in the ST T complex which results in an increased QRS-T angle in normal subjects may represent an early equivalent of the typical ST T changes rather than a qualitative difference.

Summary

The present data suggest that quantitation of the changes that occur in the ST T portion of the electrocardiogram can be used as an index of the response to digitalis in normal individuals. Numerous factors such as nonspecific T wave changes have made this a difficult area to study.

The effect of digoxin on the orthogonal ECG was observed in adult male subjects during a controlled 8-hour period and during the subsequent 4 days. The data were recorded on FM magnetic tape and analyzed by a digital computer. Two hundred different ECG measurements were examined.

The recordings in 10 subjects receiving digitalis were compared to the baseline recordings in the same subjects and to the recordings in an equal number of subjects who received normal saline (6.4 c) and

served as controls. Eight subjects were common to both groups. The spatial magnitude of the maximal T vector and the spatial magnitude of the time integral of the ST T complex provided the best index of the digitalis effect If the 6-hour response of the digitalis group is corrected for the T wave change apparent in the control group at 6 hours the temporal course showed a maximum effect at 4 hours. Two thirds of this response was evident at 30 minutes and 95 per cent of the peak response was observed 2 hours after intravenous digoxin Poorer results were obtained with the other ECG measurements, including the P R interval heart rate Q-T index and directional changes in the S-T segment and T wave

We are grateful t Mr Marvin Dick for his able technical assistance

REFERENCES

1. Pardee, H The tandardization of digitalis by its action on the human heart J A M.A. 81 186 1923
2. Berliner K. Observations on the duration of the electrical systole of the heart, with special reference to the effect of digitalis, Am. Heart J 7 189 1931
3. Brams, W and Gaberman, P The effect of digitalis on th T-wave of the electrocardiogram. An experimental tudy in human beings Am. Heart J 6:804 1931
4. Larsen, K., Neukirch, F and Nielsen, N: Electrocardiographic changes i normal adults following digitalis admi istration, Am. Heart J 13 163 1937
5. Geiger A Blaney L., and Druckemiller W A quantitative electrocardiographic study of digitalization, Am. Heart J 22:230, 1941
6. Apter L. Ashman, R. and Hull, E. A quantitative tudy of th effects of ouabain upon the electrocardiogram, J Pharmacol. & Exper Therap 82:227 1944.
7. Gold H. Kivit, N and Cattell, M Studies on purified digitalis glucosides. Potency and dosage of Digitaline nativelle by oral administration in man J Pharmacol. & Exper Therap. 69 177 1940.
8. Pipberger H Stallman, F Yano, K., nd Draper H: Digital computer analysis of the normal and abnormal electrocardiogram, Prog Cardiovas. Dis. 5:378, 1963
9. Bazett, H An analysis of the time-relations of electrocardiograms, Heart 7:353 1918.
10. Snyder J Hamlin, R. Schaal, S Goldstein, A., and Weissler A. Effect of digoxin on the spatial orientation nd integrated spatial magnitude of the T wave in normal individuals, Am J Cardiol 17 781 1966.
11. Cosma, J Levy B and Pipberger H The spatial ventricular gradient during alterations in the ventricular activation pathw y Am Heart J 71:84 1966.

Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K

*Borys Surawicz, M.D.**
*Henryk Chlebus, M.D.***
*Alberto Mazzoleni, M.D.****
Lexington, Ky.

An increase in the concentration of extracellular K to 8 to 12 mEq. per liter depressed myocardial contractility in isolated cardiac preparations.[1-4] However, in anesthetized dogs the force of right ventricular contraction and cardiac output was unchanged when the concentration of plasma K (K_p) was increased to 7.8 mEq. per liter.[5] In another study the force of left ventricular contraction was unchanged when the concentration of K was increased to 11.4 mEq. per liter.[6] In these two studies 0.6 to 3.7 mEq. of K per kilogram was administered intravenously at a rate of 0.7 mEq. per minute. We observed a decrease in systemic and right ventricular pressure after the administration of only 0.1 to 0.2 mEq. of K per kilogram into the dog pulmonary artery when the rate of administration of K was ten to fifteen times more rapid than in the above-mentioned studies. Our observations were made first in potassium-depleted dogs with hypopotassemia and confirmed subsequently also in nondepleted animals with a normal concentration of K_p. In our experiments the drop in pressure was consistently followed by an overshoot. The electrocardiographic effects of the rapid administration of K were also different from the effects of administration of K at a slower rate.

The purpose of the present study was to (1) compare the effects of various rates of administration of K on the intracardiac pressures, cardiac output, contractile force, and electrocardiogram of anesthetized dogs; (2) compare the hemodynamic and electrocardiographic effects of rapid administration of K in normal and K-depleted dogs; (3) investigate the mechanism of the depression and overshoot of contractile force produced by the rapid administration of potassium.

Material and methods

Mongrel dogs weighing from 12 to [illegible]9 kilograms were fasted overnight and then anesthetized with sodium pentobarbital (28 mg. per kilogram). The trachea was intubated using a plastic tube with an inflatable balloon cuff for the administra-

From the Cardiovascular Division, Department of Medicine, University of Kentucky College of Medicine, Lexington, Ky.

Aided by National Institutes of Health Grant HE [illegible]-04.
Received for publication June 27, [illegible].

*Professor of Medicine and Director of Cardiovascular Division, University of Kentucky College of Medicine.
**Assistant Professor, Second Medical Clinic, Warsaw, Poland.
***Assistant Professor of Medicine, University of Kentucky College of Medicine.

tion of room air by respirator at a rat of 1.0 to 1.7 liters per minute. Arterial blood pH, pO_2, and pCO_2 were determined at hourly intervals. They remained within normal limits throughout the procedure which lasted from 3 to 6 hours. Rigid plastic catheters with a lumen diameter of 2 mm. were inserted into the right femoral artery for the sampling of blood, into the right femoral vein for the intravenous administration of K or drugs, and into the aorta via the left femoral artery for the measurement of pressure. A 40-cm. long plastic catheter with a lumen diameter of 3 mm. was inserted via the right carotid artery into the left ventricle, and a similar catheter was inserted via the right jugular vein into the right ventricle for the measurement of pressure. Another 60-cm. long catheter with a lumen diameter of 2 mm. was inserted via the left jugular vein into the pulmonary artery for rapid infusions of K. The sternum was split, and after incision of the pericardium a strain-gauge arch was sutured to the left ventricle by the method of Cotten and Bay.[6] The left ventricular contractile force was expressed as a per cent of the control. A magnetic flow probe selected to fit snugly but with minimal compression was placed around the segment of the ascending aorta proximal to the origin of the large vessels.

In several experiments the heart rate was kept constant by driving the atria or the ventricles with a Grass S4 stimulator at a rate slightly higher than the spontaneous rate. The stimulating electrodes were made of sharpened silver wires plunged into the myocardium. The interelectorde distance was 10 mm. The stimulating current was slightly above threshold. Pressures were measured with Statham P23d transducers attached directly to the catheters and recorded simultaneously with the aortic flow and Leads II and V_3 on a multichannel Sanborn 350 direct-writing recorder at paper speeds ranging from 0.25 to 100 mm. per second.

The rate of change in the ventricular pressure pulses (dp/dt) was determined continuously with an R-C differentiating circuit consisting of a 1 megohm resistor and a 150-picafarad condenser. The time constant of this circuit was 100 μsec. The differential tracing was calibrated in each experiment by comparison with four to five direct measurements of the maximum slopes of the ascending portions of left ventricular pressure tracings recorded simultaneously at paper speed of 100 mm. per second. Left ventricular stroke flow was measured with a Carolina Electronics square-wave electromagnetic flowmeter and recorded by a Sanborn D.C. coupling preamplifier. The flowmeter was calibrated in situ at the end of each experiment by injecting past the probe a known volume of heparinized blood previously collected from the same dog. At least three calibration curves were recorded.

The aortic stroke flow represents the left ventricular stroke flow minus the coronary flow. The systemic peripheral resistance was calculated from the formula[7]

$$\text{Kg PRU} = \frac{Ao_m \times \text{weight}}{\text{C.O. ml./sec.}}$$

where Kg PRU expresses in Kg R units the resistance which caused a fall in pressure of 1 mm. Hg for each milliliter of blood flowing per second per kilogram tissue. Ao_m = mean aortic pressure in millimeters of mercury; weight in kilograms; C.O. mL/sec. = cardiac output in milliliters per second.

Concentrations of plasma sodium and potassium were measured by standard flame photometry. The interval from stimulus to onset of P (St-P) and the R-R, QRS, and Q-T intervals were measured with the accuracy of 0.002 second in the tracings recorded at paper speed of 100 mm. per second. With the exception of QRS duration, the measurements were rounded up to the nearest 0.01 second.

Infusions of KCl diluted in 5 per cent aqueous glucose were administered at a constant rate with a motor-driven syringe to 47 dogs on a standard chow diet (control) and to 28 dogs with hypopotassemia and K-depletion. Some dogs were pretreated with propranolol, acetyl strophanthidin, or quinidine before the infusions of KCl.

Hypopotassemia was produced by feeding the animals a diet* containing 400 to 570 mg. of K and vitamin supplement for 4 to 12 weeks. Each day the dogs received

*Supplied by Morris Research Laboratories, Topeka, Kans.

1 Gm. of chlorothiazide by mouth and 20 mg. of DOCA intramuscularly. The change in weight during the period of depletion ranged from −1.1 to +7.4 kilograms. The dogs usually developed muscular weakness or paralysis when the concentration of K was below 2.0 mEq. per liter.

The amount of KCl in the solution was determined by the weight of the dog and the type of infusion. One liter of solution contained 13.3 mEq. per kilogram for slow infusions and 32 or 48 mEq. per kilogram for rapid infusions. The slow infusions of K were made into the femoral vein at a rate of 1.7 μEq per kilogram per second. The duration of slow infusions ranged from 4 to 25 minutes (average 10 minutes) and the volume of the infused solution ranged from 30 to 190 ml. (average 75 ml.). The total amount of infused K ranged from 0.4 to 2.5 mEq. per kilogram. Samples of arterial blood for determination of the concentrations of K and Na were drawn before the infusion and at various stages of development and regression of K intoxication. Tracings were recorded at the time of sampling.

In order to deliver high concentrations of K to the heart, rapid infusions of K were made into the pulmonary artery after the dead space of the catheter had been filled with the infused solution. The rates of rapid infusions ranged from 6 to 30 μEq per kilogram per second. The duration of rapid infusions ranged from 3 to 12 seconds and the volume of the infused solution ranged from 1.8 to 7.6 ml. The amount of infused K ranged from 0.07 to 0.28 mEq. per kilogram. The rapid infusions were repeated 10 to 15 minutes after the return of the electrocardiographic pattern to control and the effects of two to four different rapid rates of administration of KCl were tested in each dog. The samples of arterial blood used for the determination of the concentration of K were collected before and immediately after the infusion. All samples were drawn within less than 10 seconds.

Propranolol (Inderal) was administered intravenously in aqueous solution as a single injection of 0.3 to 0.5 mg. per kilogram of body weight. In order to test the beta blocking effect of the drug, we compared the effect of isoproterenol in a concentration of 1 microgram per kilogram of body weight before and after the administration of propranolol. In each case 90 to 95 per cent of the effect of isoproterenol on systolic systemic pressure, pulse pressure, and heart rate was "blocked" for a period of 2 to 3 hours by pretreatment with propranolol. Rapid infusions of K were made within the first hour after the administration of propranolol.

Acetyl strophanthidin was administered in aqueous solution of 5 per cent glucose at a rate of 0.2 mg. per minute until multiple ventricular ectopic beats began to appear. The total amount of acetyl strophanthidin ranged from 0.5 to 1.0 mg. Rapid infusions of KCl were made within 7 minutes after termination of the infusion of acetyl strophanthidin.

Quinidine sulfate was administered in aqueous solution of 5 per cent glucose at a rate of 2 mg. per kilogram per minute for 20 to 30 minutes in order to produce a decrease in systolic aortic pressure to 70 to 75 mm. Hg. When the pressure decreased to this level, the QRS duration was increased twofold to threefold.

The statistical significance of the results was evaluated by determining the standard error of the difference between the means using the pooled variances formula and the student "t" test.

Results

Slow infusions of KCl. Table I presents the results of administration of KCl in nondepleted and depleted dogs with nondriven and with driven atria. In 3 additional dogs the constant rate was maintained by driving the ventricles and the results were similar to those presented in Table I. The effect of the concentration of K on the ventricular excitability threshold determined during this study was described elsewhere. Table I shows that atrial excitability threshold and latency (St-P) increased when the concentration of K exceeded 7.1 mEq. per liter. The effect of various concentrations of K on the electrocardiogram, intracardiac pressures, cardiac output, contractility, and peripheral resistance was essentially the same in dogs with driven atria as in those with nondriven atria. The rate was slightly

Table I Slow intravenous administration of KCl (1 7 µEq/Kg/sec) in 9 control

Plasma K range (mEq/L.)	*Number of dogs*	*Stimulation threshold (volts)*	*St P*	*R R*	*P R*	*QRS*	*(Q-T) − (QRS)*	*L.V. systolic*
<3 0								
Nondriven	4			46 ± 8	12 ± 1	5 0 ± 0 3	19 ± 2	101 ± 5
Driven	3	0 7 ± 0 3	4 ± 2	39 ± 4	12 ± 1	5 5 ± 0 4		85 ± 29
3 0-5 0								
Nondriven	10			51 ± 7	10 ± 2	5 0 ± 0 2	20 ± 2	97 ± 27
Driven	10	0 7 ± 0 5	4 ± 0	39 ± 5	10 ± 2	5 9 ± 0 9	18 ± 1	94 ± 28
5 1-7 0								
Nondriven	10			48 ± 7	10 ± 2	6 0 ± 0 1	18 ± 2	112 ± 22
Driven	8	0 8 ± 0 3	4 ± 1	39 ± 5	11 ± 2	6 5 ± 0 8	18 ± 2	115 ± 24
7 1-9 0	7							
Nondriven	7			46 ± 5	12 ± 1	8 6 ± 0 8	18 ± 1	144 ± 14
Driven	4	5 1 ± 2 8	7 ± 3	40 ± 2	12 ± 2	6 8 ± 1 3	15 ± 1	133 ± 31
9 1-11 0								
Nondriven	6			57 ± 6		10 9 ± 1 2	18 ± 2	124 ± 16
Driven	6	5 7 ± 5 0	6 ± 2	43 ± 2	14 ± 4	8 3 ± 3 3	16 ± 3	115 ± 30
11 1-15 0								
Nondriven	8			51 ± 8		12 7 ± 1 1	15 ± 2	126 ± 27
Driven	5	9 0 ± 5 6	7 ± 1	40 ± 5		11 4 ± 3 7	16 ± 1	116 ± 30

Average and standard deviation of electrocardiographic intervals, expressed in 0 01 second, and of hemodynamic measurements
3.0 mEq L. Eight control dogs had concentrations of K_p within the range of 3 0-5.0 mEq/L., and 1 dog, within the range of
hen the hearts were not driven Of 13 dogs with nondriven hearts, measurements were made within six ranges of K concentration
hearts measurements were made within four ranges of K concentration in 2, within three ranges in 6, and within two ranges in 3

decreased only within the range of 9 1 to 11 0 mEq per liter There was a progressive increase in the QRS duration and decrease in the duration of the (QT-QRS) interval with increasing concentrations of K_p.

The right and left ventricular diastolic pressures ranged in all experiments from 0 to 7 mm Hg Slight variations in these pressures were not related to changes in the concentration of K_p. In all dogs the ventricular systolic pressure, left ventricular dp/dt stroke volume and cardiac index were greater when the concentration of K was within the range of 7 1 to 9 0 mEq per liter than within lower ranges The statistical significance of the average differences between the 7 1-9 0 mEq/L. range and the 3 0-5 0 mEq/L. range varied from $p < 0.005$ for the left ventricular systolic pressure to $p < 0.02$ for the stroke volume with intermediate p values for the right ventricular systolic pressure left ventricular dp dt and the cardiac index. The pressure and flow returned to control values in all dogs when the infusion was discontinued and K dropped to a lower range. A possible increase in plasma volume produced by the infusion could not account for the increased pressure and flow because infusions of 250 ml of 5 per cent aqueous glucose administered at the same rate as KCl produced no appreciable hemodynamic changes. The increase in the pressures, flow and left ventricular dp/dt above the control values persisted in some dogs even when the concentration of K was within the highest range but in other dogs the values declined approaching the control. The average left and right ventricular systolic pressures and cardiac output were somewhat greater with the highest concentrations of K than with concentrations of K_p below 7 0 mEq per liter but the difference was not statistically significant. Fig 1 shows that a threefold increase in QRS duration accompanying hyperpotassemia had no deleterious effect on the pressure stroke volume and the force of left ventricular contraction

The left ventricular contractile force measured by the strain-gauge arch was greater within the 7 1-9 0 mEq/L. range

and 4 K-depleted dogs

R.V. systolic	Aortic diastolic	L.V. dp/dt max. (mm. Hg/sec. × 10³)	L.V. contraction (% of control)	Cardiac index (ml./min./Kg.)	L.V. stroke volume (ml.)	Kg. PRUs (Kg. R units)
20 ± 2	75 ± 12	2 3 ± 0 5	101 7 ± 2 0	104 ± 13	11 6 ± 0 9	50 2 ± 10 4
21 ± 3	66 ± 19	1 8 ± 0 9	108 0 ± 3 9	84 ± 4	7 4 ± 1 0	52 0 ± 19 0
24 ± 1	72 ± 15	2 2 ± 0 6	100 0 ± 0 0	95 ± 19	14 0 ± 2 8	49 9 ± 13 4
23 ± 1	71 ± 9	2 1 ± 0 7	100 0 ± 0 0	95 ± 16	11 0 ± 2 5	45 8 ± 11 9
21 ± 5	81 ± 11	2 8 ± 1 1	102 5 ± 9 8	95 ± 32	14 3 ± 4 1	64 3 ± 5 6
26 ± 1	80 ± 13	2 9 ± 0 8	109 6 ± 11 0	100 ± 21	12 9 ± 3 5	60 9 ± 22 1
34 ± 6	116 ± 23	3 2 ± 0 6	136 2 ± 10 0	139 ± 39	17 6 ± 4 4	60 9 ± 13 4
29 ± 3	106 ± 23	3 1 ± 1 1	102 3 ± 10 0	116 ± 33	14 3 ± 2 4	64 1 ± 33 2
30 ± 3	80 ± 19	2 6 ± 1 4	95 7 ± 32 5	99 ± 27	11 9 ± 5 8	68 7 ± 6 4
31 ± 4	90 ± 19	2 5 ± 1 4	96 2 ± 10 8	114 ± 49	13 7 ± 3 4	67 4 ± 10 5
27 ± 1	90 ± 16	2 7 ± 1 2	99 9 ± 16 0	110 ± 40	16 6 ± 4 2	66 8 ± 2 7
25 ± 2	90 ± 18	2 9 ± 1 3	95 2 ± 12 4	89 ± 13	12 5 ± 5 6	80 1 ± 23 8

Asterisks indicate intervals which could not be accurately measured. All K-depleted animals had concentrations of K_p below 7 mEq./L. In 11 of 13 dogs, measurements were made both when the hearts were driven and when not driven, in 2 dogs, only in 1 within five ranges in within four ranges in 4, within three ranges in 4, and within two ranges in 3. Of 1 dogs with driven

than within the 3 0-5 0 mEq./L. range in 4 dogs, but smaller in 2 dogs and unchanged in 1. Table I shows that the average contractile force was maximal when K_p was within the 7 1-9 0 mEq./L. range but because of a large scatter of values the difference between this and other ranges of K_p concentration was not statistically significant. The peripheral resistance tended to increase with increasing K. However the difference between different ranges of K concentration was not statistically significant because of a large scatter of values. The effects of infusions of KCl were reproducible during repeated infusions in 8 of 9 dogs.

Rapid infusion of KCl. The order in which the infusions were made had no effect on the results and the results were reproducible with repeated infusions. In order to facilitate the presentation of the results the rates of rapid infusion were broken down into two categories the "slower" (6-15 μEq/Kg./sec.) and the "faster" (20-35 μEq/Kg./sec.) The amount of K administered at slower rates ranged from 0 07 to 0.15 mEq per kilogram and averaged 0 11 mEq per kilogram. The amount of K administered at faster rates ranged from 0 10 to 0 35 mEq per kilogram and averaged 0 2 mEq per kilogram. The detailed results of the effects of slower and faster rates of infusion of KCl in nondepleted dogs and of faster rates in K-depleted dogs are presented in Table II.

A. ELECTROCARDIOGRAM. The effect of rapid infusions of KCl on the electrocardiogram can be subdivided into three phases. At first, the heart rate, QRS duration and the (QT-QRS) interval decreased; this phase was followed by the development of a typical electrocardiographic pattern of hyperpotassemia, and then there was a gradual return to the control.

B. HEMODYNAMIC CHANGES. The hemodynamic response to rapid infusions of KCl also consisted of three distinct phases. At first, the left ventricular and right ventricular systolic pressures, the aortic diastolic pressure, the left ventricular dp/dt, the stroke volume and the left ventricular contractile force decreased

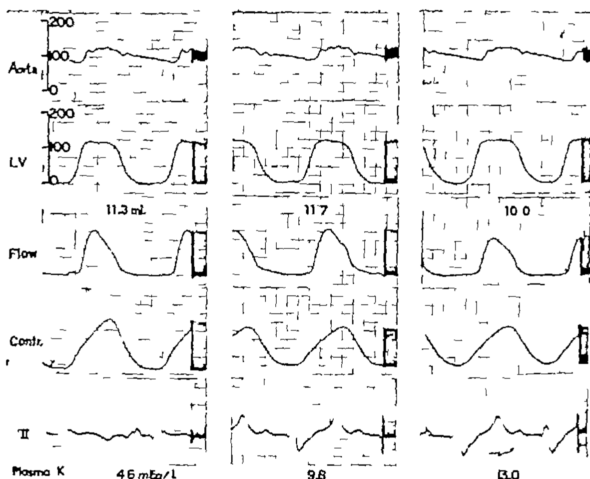


Fig. 1. *From top to bottom:* Aortic pressure (*Aorta*), in mm. Hg; left ventricular pressure (*LV*), in mm. Hg; aortic stroke volume (*flow*), ml; left ventricular contractile force (*Contr.*), and Lead II before and during intravenous administration of KCl at rate of 1.7 μEq/Kg./sec. in 18-kilogram dog. Constant rate maintained by driving the right atrium. Excitability threshold at K 4.6 mEq./L. = 0.36 volt, at 9.8 mEq./L. = 5.4 volt, and at 13.0 mEq./L. = 6.2 volt. Note that when the QRS duration increases from 0.05 sec. at K concentration 4.6 mEq./L. to 0.15 sec. at K concentration 13.0 mEq./L., the left ventricular and aortic pressures are unchanged, whereas the stroke volume and the force of left ventricular contraction are only slightly decreased. Paper speed 100 mm./sec.

Table II. Rapid administration of KCl into pulmonary artery (6 35 μEq/Kg./sec.)

Experiment	Rate of K administration (μEq/Kg./sec.)	Number of dogs	Plasma K (mEq./L.)		ECG intervals (0.1 sec.)				
			Initial	Peak	Max. R-R increase	Max. P-R increase	Max. QRS decrease	Max. QRS increase	Max. (QT)-(QRS) decrease
Nondepleted	6-15	12	4 2 ± 0 7	9 2 ± 2 3	11 ± 13	1 ± 1	1 ± 06	2 ± 2	5 1
Nondepleted	20-33	12	4 3 ± 0 8	11 2 ± 3 5	40 ± 45	2 3	1 ± 0 6	5 6	8 ± 5
K-depleted	20-33	12	2 0 ± 0 9	10 4 ± 3 4	112 ± 123	2 ± 3	3 ± 0 6	2 ± 3	10 ± 6
Nondepleted after propranolol	20-33	4	3 7 ± 0 1	11 2 ± 5 5	240 ± 199	6 ± 3	2 ± 0 9	14 ± 4	13 ± 7

Average and standard deviations of electrocardiographic intervals, left ventricular (L.V.) systolic pressure, aortic diastolic pressure, …

The depression of the right ventricular pressure was usually less pronounced than that of the left ventricular pressure. The initial depression was followed by a phase of overshoot and then a gradual return to control. A typical experiment is illustrated in Fig. 2. The depression lasted usually throughout the first and part of the second phases of the electrocardiographic changes and the maximal depression usually occurred at the time of maximal decrease in heart rate and maximal shortening of the QRS and (QT-QRS) intervals. However, the time of onset, the duration and the peak of the overshoot were not related to the heart rate or to the electrocardiographic pattern. The end-diastolic left and right ventricular pressures or the right atrial pressures were not significantly changed during the depression. During the overshoot, the end-diastolic right and left ventricular pressures were unchanged or increased.

When the atria were driven, A-V block occurred during the first phase (Fig. 3). When the ventricles were driven with suprathreshold stimuli, the typical hemodynamic response to rapid infusion of KCl occurred in the absence of changes in heart rate (Fig. 4).

Table II demonstrates that the "faster" rates of infusion produced a *higher* peak concentration of K_p, a greater slowing of the heart rate ($p < 0.05$), a greater and longer-lasting depression ($p < 0.0?$) and a greater and longer lasting overshoot ($p < 0.05$) than did the "slower" rates. With the "slower" rates of infusion the duration of depression equaled the duration of overshoot, and the number of beats with depressed contraction equaled the number of beats with the overshoot. However, with the "faster" rates of infusion the duration of the overshoot was longer than the duration of depression.

C. K-DEPLETED DOGS. In hypopotassemic K-depleted dogs with concentrations of K ranging from 1.6 to 2.8 mEq per liter the administration at "slower" rates produced a lower peak concentration of plasma K (average 6.0 ± 1.5 mEq per liter) than in the nondepleted dogs. However, the hemodynamic response to the infusions at "slower" rates was the same as in nondepleted dogs. The detailed results of these experiments are omitted. Table II shows that, with faster rates of administration of K the K-depleted dogs developed a greater initial shortening of the QRS interval ($p < 0.001$) and a greater slowing of the heart rate ($p < 0.05$) than did the nondepleted dogs. The depression of the left ventricular systolic and aortic diastolic pressures was also greater in the K-depleted dogs ($p < 0.05$). However, there was no significant difference in the magnitude and duration of the overshoot between the K-depleted and the non-depleted dogs.

D. LETHAL INFUSIONS. Ten dogs died after the administration of 0.21 to 0.3 mEq of K per kilogram of body weight

L.V. systolic pressure (mm. Hg)		*Aortic diastolic pressure (mm. Hg)*		*Number of beats*		*Duration (sec.)*	
Max. decrease	*Max. overshoot*	*Max. decrease*	*Max. overshoot*	*Depression*	*Overshoot*	*Depression*	*Overshoot*
11 ± 11	40 ± 27	7 ± 4	11 ± 8	25 ± 7	29 ± [illegible]	14 [illegible] 6	13 ± 2
25 ± 22	34 ± 29	21 ± 23	23 ± 9	34 ± 18	95 ± 44	17 ± 7	55 ± 40
24 ± 25	22 ± 13	20 ± 25	36 ± 17	25 ± 12	178 [illegible] 74	19 ± 4	70 ± 43
34 ± 13	90 ± 32	82 ± 19	48 ± 21	88 ± 25	192 ± 23	51 [illegible] 25	124 ± 21

depression and overshoot of the L.V. systolic pressure.



Fig. 2. From top to bottom: Left ventricular systolic pressure (*L.V.*) in mm. Hg, left ventricular dp/dt, aortic pressure (*A.*) in mm. Hg, right ventricular pressure (*R.V.*), in mm. Hg, and Lead II during and after the administration of 2.2 mEq. of KCl to the pulmonary artery of a 20-kilogram dog within 9 seconds. Time in seconds after the onset of infusion (0 sec.). K concentration before infusion 4.4 *m*Eq./L. and after infusion 9.4 mEq./L. Paper speeds 10 mm./sec. and 2.5 mm./sec. in part of the section between 130 and 150 seconds. Note the decrease, the overshoot, and the return to control of the left and right ventricular systolic pressures, the aortic systolic and diastolic pressures, and the left ventricular dp/dt. See text.

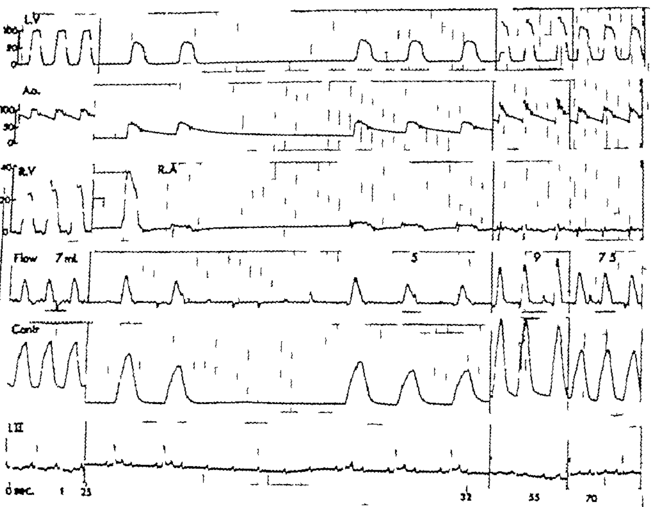


Fig. 3. Adm[illegible] of 3.45 ml [illegible] of KCl [illegible] the pulmonary artery of 13.5-k[illegible] K-depleted dog w[illegible] 9 sec and 1 m[illegible] second [illegible]fter the onset of infusion (0 [illegible] Righ[illegible] [illegible] of 2.1/sec. Concent[illegible]tion of K before infusion 2.8 [illegible]Eq./l [illegible]nd [illegible]fter infusion 8.0 mEq./L. Abbreviations as in Figs. 1 and 2. During [illegible] righ[illegible] entric[illegible]lar pressure the [illegible]theter was withdr[illegible]wn to the right [illegible]trium (R.A.). [illegible] per speed 25 mm./sec. Not[illegible] the A-V bl[illegible] [illegible] be depressi[illegible] [illegible] the [illegible] the decreased left ventricular [illegible] tolic and aortic pressures and flow. The depression is followed by overshoot and the [illegible] ventricles.

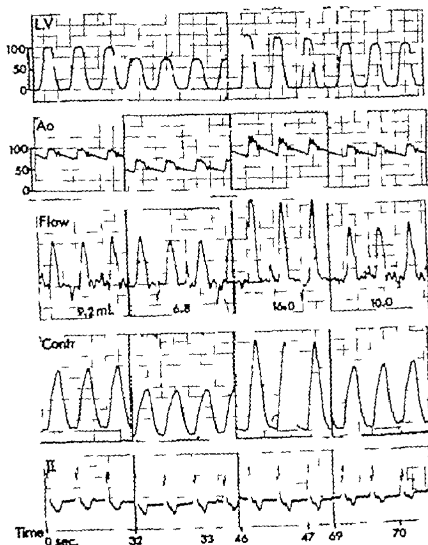


Fig. 4. Administration of 3.45 mEq. of KCl into the pulmonary artery of the same dog as in Fig. 3 within 9 seconds. Right ventricle driven at a rate of 2/sec. Time in seconds after the onset of infusion (0 sec.). Concentration of K before infusion, 3.1 mEq./L.; after infusion, 9.0 mEq./L. Abbreviations as in Fig. 1. Paper speed 25 mm./sec. Note the constant ventricular rate, the depression, the overshoot, and the return to control of the left ventricular systolic, aortic systolic, and diastolic pressures, flow, and the contractile force. See text.

at a rate of 30 to 35 μEq. per kilogram per second, 9 with ventricular fibrillation and 1 with ventricular standstill. Fibrillation developed within 14 to 150 seconds (average 51 seconds) after the onset of infusion. The concentrations of K after lethal infusions ranged from 14.0 to 25.0 mEq. per liter. The highest concentration of K recorded in a dog which survived the infusion and did not develop fibrillation was 20.0 mEq. per liter.

C. PRETREATMENT WITH PROPRANOLOL. Propranolol had no significant effect on the concentration of K and the aortic diastolic pressure, but slightly increased the R-R, P-R, QRS, and (QT-QRS) intervals, and decreased the left ventricular systolic pressure and the dp/dt. Table II shows that the administration of K in dogs pretreated with propranolol produced the same increase in the concentration of K as in the control. However, in the dogs pretreated with propranolol all electrocardiographic effects were exaggerated, the magnitude and duration of left ventricular systolic pressure depression was

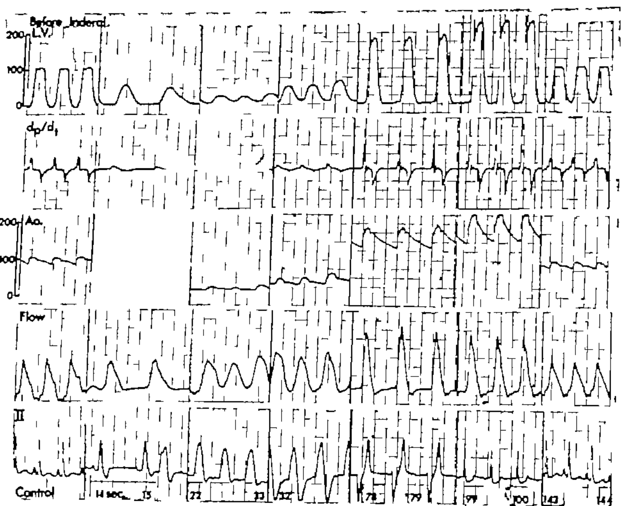


Fig. 3. Administration of 3.0 mEq. of KCl i t the pulmonary rtery of 16.5-kilogram dog withi 6 seconds. Time i seconds after the onset of infusion. Abbreviations as Figs. 1 nd 2. per peed 25 mm./sec. See text

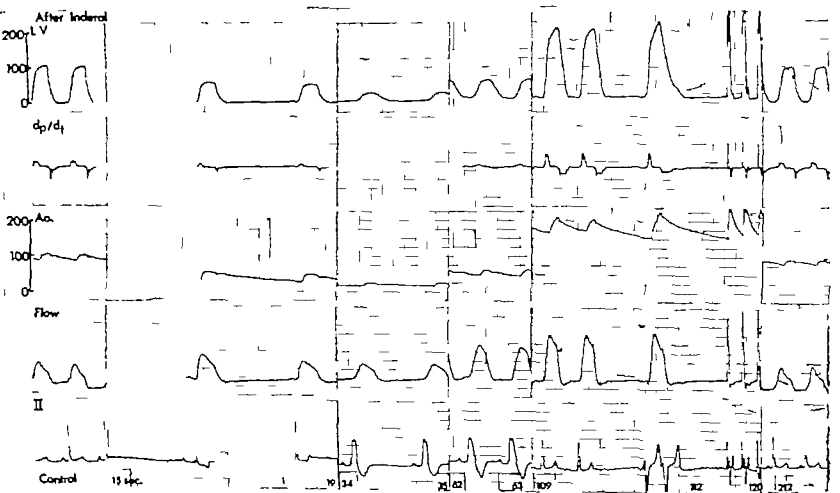


Fig. 6 Same experiment as I Fig. 7 in the same dog after pretreatment with 6.5 mg of propranolol (Inderal). Note the slower rate, the decreased left ventricular dp/dt, and the decreased aortic flow after propranolol. Note that th administration of K produces greater slowing of the heart rat and a longer lasting decrease l pressure and flow than in the control (Fig. 5). Note the presence of overshoot. See text.

greater ($p < 0.001$) and the overshoot lasted longer ($p < 0.05$). The magnitude of the overshoot was approximately the same as in the control. In 2 dogs, identical infusions of KCl were made before and after propranolol. One of these experiments is illustrated in Figs. 5 and 6.

F. PRETREATMENT WITH ACETYL STROPHANTHIDIN. In 2 dogs the effect of rapid administration of KCl was compared before and after the administration of acetyl strophanthidin. Acetyl strophanthidin increased the left ventricular dp/dt by 40 per cent in one dog and by 60 per cent in the other dog. In both animals the administration of KCl before and after acetylstrophanthidin produced similar increases in the concentration of K_p. However, after acetyl strophanthidin the bradycardia was more pronounced. Thus, the maximum R-R before acetyl strophanthidin was 0.68 second in both dogs, and increased after acetyl strophanthidin to 2.7 seconds in one and to 2.04 seconds in the other. The P-R interval was slightly longer and the (QT-QRS) interval shorter after acetyl strophanthidin. After acetyl strophanthidin the depression of left ventricular contractile force, the decrease in left ventricular systolic and diastolic pressures, and the magnitude and duration of the overshoot were more pronounced in both animals. An illustrative experiment is presented in Fig. 7.

G. PRETREATMENT WITH QUINIDINE. The effect of "faster" rates of rapid administration of KCl on the electrocardiogram and aortic pressure was tested in 5 dogs after the administration of toxic doses of quinidine. Administration of KCl markedly potentiated the electrocardiographic manifestations of quinidine toxicity. However, the systolic and diastolic pressures were not significantly affected, and there was no overshoot (Fig. 8).

Discussion

Our study demonstrated that marked intraventricular conduction disturbance produced by hyperpotassemia had no demonstrable adverse effect on the ventricular pressures, cardiac output, and force of contraction. The progressive increase in QRS duration in hyperpotassemia occurs usually without a change in the QRS shape.[8] This suggests that unlike that in the case of ventricular premature beats or bundle branch block, the QRS widening in hyperpotassemia may not be accompanied by a change in the sequence of depolarization in the ventricles. Thus, the maintenance of normal force of contraction may be due to maintenance of an orderly sequence of activation of the contractile elements.

Although the average contractile force measured by the strain-gauge arch was approximately the same at all concentrations of plasma K, the maximum cardiac output, left and right ventricular systolic pressures, and left ventricular dp/dt were recorded when the concentrations of K ranged between 7 and 9 mEq. per liter. This was suggestive of increased contractility within this K range because in the majority of dogs the heart rate, the end-diastolic left ventricular pressure, and the peripheral resistance were not changed. Whether these results are applicable to a hyperpotassemic man is uncertain. In dogs, the hyperpotassemia was produced rapidly with relatively small amounts of potassium which were not expected to alter appreciably the concentration of intracellular K in the myocardium. In patients with hyperpotassemia the retention of K may be more chronic and may therefore be accompanied by changes in the concentration of intracellular K in the myocardium.

The hemodynamics of the K-depleted hypopotassemic dogs were approximatel[y] the same as those of the nondepl[e]ted dog with concentrations of K rang[i]ng fro[m] 5 to 7 mEq. per l[i]ter. This is [i]n keeping w[i]th the observations of Sm[i]th [a]nd associates that dogs w[i]th se[v]ere depletion of K, muscular paral[y]sis, and degenerat[iv]e changes in th[e] skeletal mus[c]le h[a]ve no demonstrable structur[a]l abnormal[i]ties of the myocardium.

The atrial ex[c]it[ab]il[i]ty threshold wa[s] sharply increased when th[e] concentrations of K exceeded about 7.0 mEq. per liter. The same was true of the ventricular excitabil[i]ty threshold in this and [i]n other studies.

During th[e] slow [i]nfusions of K, h[y]perpotassemia was accompanied by only a slight decrease in heart rat[e]. The [m]in-

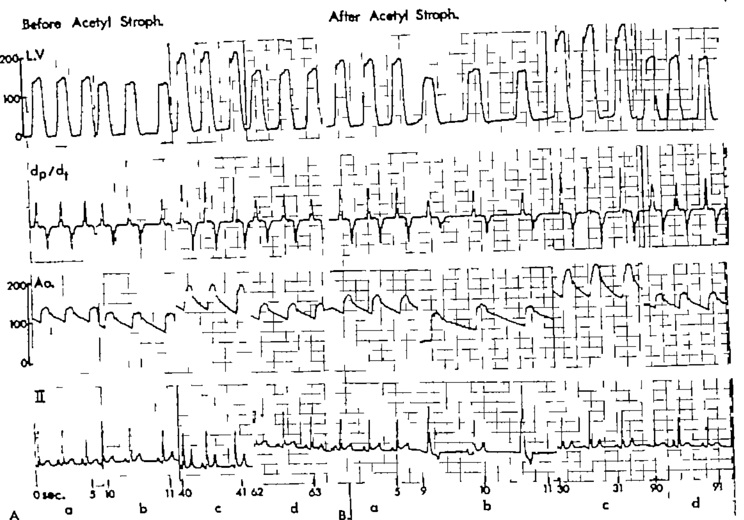


Fig. 7. Administration of 4.6 mEq. of KCl into the pulmonary artery of a 20 kilogram dog within 7.5 seconds before (A) pretreatment with 0.7 mg. of acetyl strophanthidin; B, after treatment. Time in seconds after the onset of infusions of KCl. Control (a); depression (b); overshoot (c); return to control (d). In A, initial K = 4.4 mEq./L.; after KCl, K = 6.4 mEq./L. In B, initial K = 5.0 mEq./L.; after KCl, K = 8.0 mEq./L. Paper speed 25 mm./sec. Abbreviations as in Figs. 1 and 2. See text.

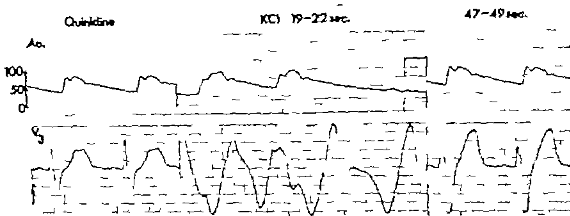


Fig. 8. Aortic pressure (Ao.), in mm. Hg and Lead V5 in an 18-kilogram dog after intravenous administration of 720 mg. of quinidine sulfate for 20 minutes. Before KCl (*left*), at the time of expected depression (*middle*), and at the time of expected overshoot (*right*), after an infusion of 2.4 mEq. of KCl into the pulmonary artery in 9 seconds. Note that infusion of KCl causes no appreciable changes in aortic pressure, whereas the electrocardiographic manifestations of quinidine toxicity are more pronounced. Paper speed 25 mm./sec.

was found in anesthetized dogs by Muller and associates.[11] The decrease in rate observed after rapid infusions of K appeared to be related more to the rate of change in the concentration of K than to an absolute increase in the concentration of K_e. Bradycardia and A-V block were observed in isolated hearts after a rapid change from a low to a "normal" concentration of K and were attributed to a depression of spontaneous depolarization in the pacemaker fibers.[12] In this study the depression of heart rate was more pronounced in hypopotassemic K-depleted animals. The possible inhibition of pacemaker fibers by a sudden increase in the concentration of extracellular K in K-depleted animals helps to explain an occasional bradycardia or A-V block during rapid infusions of K salts in patients with hypopotassemia. Swales[*] reported bradycardia and A-V block in a severely K-depleted patient during the administration of KCl at a rate of 50 to 60 mEq. per minute. In that case the atrial and the ventricular ECG complexes showed no pattern of hyperpotassemia at the time of A-V block or immediately after the cessation of the infusion of KCl.

The effect of K on QRS duration depends on the rate of administration. The progressive increase in QRS duration during the slow infusion was attributed to a decreased conduction velocity caused by the slowing of the upstroke velocity of the ventricular action potential resulting from a decrease in the resting membrane potential. During rapid administration of K the increase in QRS duration was preceded by a decreased QRS duration. Moderate increases in the concentration of extracellular K increased the intraventricular conduction velocity.[14] A decrease in QRS duration after a rapid change from a low to a normal concentration of K in perfused rabbit hearts was attributed to a reduction in the difference between the resting and threshold potentials.[13] The same mechanism could explain the decrease in QRS duration observed after a rapid increase in the concentration of K_e.

A decreased duration of ventricular repolarization accompanied both the slow and the rapid increases in the concentration of K_e, but was more pronounced during rapid infusions. Weidmann demonstrated that, when the concentration of extracellular K was abruptly raised after the onset of depolarization, the velocity of repolarization increased. A very marked decrease in the duration of the ventricular action potential was observed after a sudden change from a low to a normal concentration of K in the perfused rabbit heart.[13]

*Unpublished observations.

The shortening of repolarization is attributed to an increased conductance of K. Our results are best explained by the assumption that the conductance of K is increased more by a rapid than by a slow increase in the concentration of K_p.

The depression of contractile force also appeared to be related to the rate of increase in K rather than to the absolute concentration of K. During slow infusions of K the contractile force was not depressed even when the concentration of K was as high as that which accompanied the depressed force of contraction observed during rapid infusions of K. To be sure the concentrations of arterial plasma K after rapid infusion into the pulmonary artery may not reflect accurately the peak concentration of plasma K in the coronary arteries. Our sample represented an average arterial concentration during the first and possibly during part of the second circulation of the infused potassium. The calculated expected maximal increase in K after the infusion assuming standard values for circulation time and plasma volume, was usually 1 to 3 mEq. per liter higher than the concentrations of arterial K in our samples. However even the calculated peak concentrations of arterial K were usually below 15 mEq. per liter and therefore still within the range in which the contractile force was not decreased during slow infusions of K.

The depression of contractile force was not related to the duration of the QRS complex, the duration of repolarization or the heart rate. The explanation of the mechanism of the depression and the subsequent overshoot of contractile force must await a better understanding of the biochemical processes underlying the excitation-contraction coupling and the mechanics of contraction. However, our findings suggest that the depression and the overshoot were caused by a direct effect of potassium on the contractile system. This appeared to be a very powerful effect, because the depression was not prevented by pretreatment with acetyl strophanthidin. When the contractile force was depressed by potassium, there was usually no increase in stroke volume or dp/dt after a longer diastole or after a premature beat. This suggests that the mechanisms which ordinarily increase the contractile force do not operate when the latter is depressed by potassium. Conversely, the blockade of cardiac beta receptors which ordinarily depresses the contractile force did not prevent the overshoot.

Recent work of Sarnoff and associates[17,41] offers evidence of the parallelism between increased contractility and increased loss of K in an isolated supported dog heart. In the same preparation Sarnoff and colleagues[17] also demonstrated a decreased contractility when KCl was infused into a coronary artery and showed that myocardial uptake of K was increased when the contractility was decreased. An infusion of KCl which resulted in a net uptake by the heart of approximately 0.1 mEq. of K substantially decreased contractility.[9]

Our results could be explained by an assumption that during the rapid increase in the concentration of extracellular K, K ions enter the cell and depress contraction by interaction with actomyosin as proposed by Szent-Gyorgyi and Hajdu.[39] The overshoot may be attributed to the increased efflux of K that accompanies the extrusion of the accumulated excess of K ions. This hypothesis would explain most of our observations on the relationship between the depression and the overshoot. With faster rates of administration of K one would expect a greater uptake of K by the cells and subsequently a greater efflux of K, hence a greater depression of contractile force, and subsequently a greater overshoot. It is reasonable to assume that cells depleted of K by our regimen or by digitalis would take up K more avidly during rapid administration, hence the greater depression in the K-depleted dogs and after acetyl strophanthidin. The lack of a concomitant increase in the overshoot in K-depleted dogs and after acetyl strophanthidin may be explained by the presence of a ceiling above which an overshoot does not increase. After quinidine the concentration of intracellular K is reportedly increased,[22] presumably because quinidine inhibits the efflux of K.[23] If the depression of contraction by quinidine is related to the increased concentration of intracellular K, a further depression may not be pos-

sible even during a rapid increase in the concentration of K_p. On the other hand the absence of overshoot may be attributed to the inhibition of the efflux of K by quinidine. An increased depression of contraction after pretreatment with a beta-blocking agent suggests that the direct effect of K may to some extent be counteracted by the sympathetic activity

Bradycardia must be considered as a possible factor contributing to the depression of contractile force, because the efflux of K is increased during the action potential.[33] With fewer heartbeats the opportunity to extrude potassium decreases and the extracellular uptake may increase. This may be partly responsible for the augmented depression in K-depleted animals, and after pretreatment with acetyl strophanthidin and propranolol

A rapid increase in the concentration of extracellular K may possibly occur after myocardial infarction trauma or severe exertion Whether the magnitude and rapidity of the increase in such situations can produce a depression of contraction in the intact animal or man remains to be established It is of interest that in experimental tourniquet shock, the release of the tourniquet was accompanied by a rapid increase in the concentration of K_p, bradycardia and a drastically lowered pressure.[34] The combination of bradycardia and depressed myocardial contractility after a rapid increase in the concentration of K must be considered to be a potentially lethal mechanism that deserves further exploration

Summary

The effects of slow and rapid rates of administration of potassium (K) on the electrocardiogram intracardiac pressures, cardiac output, and left ventricular contractile force were studied in K-depleted and nondepleted dogs. The slow infusions of KCl were administered intravenously at a rate of 1 7 µEq per kilogram per second for 4 to 25 minutes, and the rapid infusions were administered into the pulmonary artery at a rate of 6 to 35 µEq per kilogram per second for 3 to 12 seconds. Comparable peak concentrations of arterial plasma K were produced by both methods.

After rapid infusions, the typical electrocardiographic manifestations of hyperpotassemia were preceded by bradycardia decreased QRS duration, and a marked shortening of the (QT-QRS) interval These effects were more pronounced in K-depleted hypopotassemic dogs

Intracardiac pressures cardiac output, and the force of left ventricular contraction remained unchanged when the concentration of plasma K was as low as 1 6 mEq per liter or as high as 15 0 mEq per liter The ventricular systolic pressures aortic diastolic pressure cardiac output and left ventricular dp/dt were maximal within the range of plasma K concentration of 7 9 mEq per liter

Rapid infusions of K produced a depression of contractile force. The depression was followed by an overshoot. A greater and a longer depression was usually followed by a greater and a longer overshoot. The depression and the overshoot were not related to the changes in heart rate or the electrocardiographic pattern. The depression was more pronounced in K depleted hypopotassemic dogs and after pretreatment with acetyl strophanthidin or propranolol The overshoot was not abolished by pretreatment with either acetyl strophanthidin or propranolol The depression and the overshoot were absent during intoxication with quinidine The depression and the overshoot were attributed to a direct effect of K on the contractile system. The combination of bradycardia and myocardial depression produced by a rapid increase in the concentration of plasma K should be considered to be a potentially lethal mechanism

Propranolol (Inderal) kindly supplied by Ayerst Laboratories, Inc New York N Y and acetyl strophanthidin by Eli Lilly & Company Indianapolis, Ind

REFERENCES

1 Garb, S The effect of potassium ammonium calcium, sodium and magnesium on the electrogram and myogram of mammalian heart muscle J Pharmacol & Exper Therap 101 317 1951
2 LaVeen H H Schatman, B H and Mdkowitz H Effects of digitalis on potassium tonus in isolated turtle heart Proc Soc Exper Biol & Med 100:538, 1959
3 Leigh L Roush G Rafi E and McGaff C J The effect of intravenous potassium on myocardial contractility and cardiac dynamics Am J Cardiol 12:686, 1963

4. Goodyer A. V. N. Goodkind, M. J. and Stanley E. J. The effects of abnormal concentrations of the serum electrolytes on left ventricular function the intact animal, Am. Heart J 67 779 1964
5. Surawicz, B. and Mazzoleni, A. Role of potassium in ve tricular a systole, Surawicz, B. and Pellegrino, E. D. editors Sudden cardiac death, New York 1964 Grune & Stratton Inc p. 90.
6. Cotten M deV and Ba E Direct measurement of changes in ardiac contractile force Am. J Ph siol 187 122 1956
7. B rd, P Medical phy iology St Louis, 1961 The C. V. Mosby Compa y p 145
8. Surawicz, B Chlebus, H Reeves, J T and Gettes, L. S Increase of entricular excitab lity threshold by hyperpotassemia J.A.M.A. 101 1049 1965
9. Gettes, L. S Surawic B and Shiue J C Effect of high K, low K nd quinidine on QRS duration nd ventricular action potential, Am J Phys iol 203 1135 1962
10. Smith, S G Black Schaffer B and Lasater T E. Potass um deficiency syndrome in the rat nd the dog Arch Path. 49 185 1950.
11. Muller O F DeLeon A. C J nd Bellet, S The effect of h perpotassemia on the idioentric lar pacem ker in complet A V heart block nd comparison ith its effect on the heart rate in normal us rh thm, Am J C rdiol. 7:817 1961
12. S les, J D Hypokalemia nd the electrocardiogram Lancet 2 1365 1964
13. Sura icz, B and Gettes L. S Tw mechanisms of cardiac arrest produced by potassium Circulation Res 12:415 1963.
14. Bammer H and Rothsch h K. E. Über die Erreg ngsleitung im Froschherz treifen unter der Wirkung on Kalium-Ionen nd anderen herzmuskelergenen Substanzen Ztschr ges exper Med 119:402, 1952
15. Han, J de J ton, I G and Moe G K Adrenergic effects on ventricula vulnerability Circulation Res. 14:516, 1964
16. Weidmann, S.: Shortening of the cardiac action potential due to a brief injection of KCl following the onset of activity J Physiol. 132 157 1956.
17. Sarnoff S. J Gilmore J P Mitchell, J H and Remensnyder J P Potassium changes in the heart during homeometric autoregulation nd acetyl tropha thid Am J Med. 34:440, 1963
18. Sarnoff S. J Gilmore J P Dagget, W M Mansfield I B., McDonald, R. H., J and Weisf ldt M L. N t potassium loss and changes in oxygen and ventricular performance during paired timulation of the heart, Bull New York Acad. Med. 41:602 1965.
19. Sarnoff S. J Gilmore J P and Wallace, A. G. The influence of tonomic nerve activity on adaptive mechanisms in the heart *In* Randall, W C editor: Nervous control of the heart, Baltimore, 1965 Williams & Wilkins Co., p. 54
20. Leonard, E., and Hajd S Action of electrolytes and drugs on the contractile mechanism of the cardiac muscle cell, Handbook of physiology Section 2 Circulation, Vol. I p. 151 Baltimore, 1962, Williams & Wilkins Co.
21. Conn, H. L. nd Wood, J C. Acute effect of quinidine on K exchange nd distribution in the dog ventricle, Am. J Phy iol. 199 151 1960.
22. Kle R L., Holland D C., a d Tinsley B Quinidine and unidirectional cation fluxes in tria Circulation Res. 8:246 1960.
23. Lorber V W lker J L. Jr Greene E. A., Mlnarik, M H and Pak, M J: Phasic efflux of potassium from frog ventricle Am J Physiol 203:253 1962.
24. Rowe D F Bennett A. L., nd McIntyre, A. R: Serum potassi m concentration and use of ouabain i experimental tourniquet shock, Am. J Physiol. 189:603 1957

Cardiac output and pulmonary blood volume in dogs
Comparison of three indicator-dilution methods

Gilberto Sanchez, M.D.
Antonio C. Quiroz, M.D.
George E. Burch, M.D.
Nicholas P. DePasquale, M.D.
New Orleans, La.

In spite of limitations, but because of its convenience, the indicator-dilution method is widely used in the estimation of cardiac output. According to the Stewart-Hamilton principle,[1,2] if a known concentration of indicator is injected rapidly into the central circulation, cardiac output can be estimated from the indicator time-concentration curve inscribed during continuous sampling from a peripheral artery. Furthermore, the mean transit time of the indicator from the site of injection to the site of sampling multiplied by cardiac output represents the circulating blood volume between the two sites.

Several techniques for estimating pulmonary mean transit time have been described.[3-6] These techniques differ primarily in the site in the circulation at which indicator is injected and withdrawn. However, since cardiac output as well as pulmonary mean transit time are estimated from the indicator time-concentration curve, the various techniques differ not only in the calculation of pulmonary mean transit time but in the calculation of cardiac output as well.

The purpose of the present study was to compare cardiac output and pulmonary blood volume determined in each of 15 dogs by means of three indicator-dilution techniques as well as by the Fick principle.

Material and methods

Cardiac output and pulmonary blood volume were determined in 15 adult mongrel dogs whose weight ranged from 16.2 to 20.0 kilograms. The dogs were anesthetized lightly with intravenous urethane (1.5 Gm. per kilogram). After the insertion of an endotracheal tube the dogs were taped supine on a flat fluoroscopic table and administered 100 per cent oxygen mixed with room air at a constant rate of 3 L. per minute.

Three red Kifa catheters of the same length, internal diameter, and volume (0.75 ml.) were positioned as follows: (1) in the pulmonary artery just distal to the pulmonic valve, (2) in the superior vena cava, and (3) in the femoral artery. A yellow Kifa catheter was passed transseptally into the left atrium. With the aid of the pressure tracing and fluoroscopic

From the Department of Medicine, Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, La.
Supported by grants from the United States Public Health Service, Rowell ... Billups Fund for Research in Heart Disease, and the Rudolph Matas Fund for the Kate Prewitt Hess Laboratory.
Received for publication June 29, 1966.
Address: Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La. 70112.

control the tip of the catheter was positioned carefully just at the atrial side of the mitral valve.

Dye-dilution curves were recorded by means of two similarly calibrated Gilford densitometers with single-stage amplifiers whose outputs were fed into D C amplifiers of a multichannel Electronics for Medicine oscillographic recorder Calibrations were made by passing known concentrations of dye-labeled blood through the densitometers connected in series. The outputs of both densitometers were found to be linear and a full-scale deflection was obtained with a dye concentration of 2 5 mg per liter Constant withdrawal at a rate of 0 42 ml. per second was made by use of a Harvard infusion withdrawal pump (Model 600-930)

Indocyanine dye (Cardio-Green) 1 0 to 1 6 ml of 1 25 mg per ml was introduced instantaneously into the circulation using a Cornwall syringe with the automatic pipetting device removed. The exact amount of dye injected was determined by subtracting the volume of dye in the catheter from the total volume of dye injected Cardiac output and mean transit time were calculated from the dye-dilution curves as described by Hamilton Moore, Kinsman and Spurling Calculated catheter delays (transit time in seconds from the tip of the catheter to the cuvettes) were subtracted from the respective determinations of mean transit time.

Cardiac output and pulmonary blood volume were determined in each of the 15 dogs utilizing three previously described methods, as follows

In *Method I* indicator was injected into the pulmonary artery (PA) and sampled from the left atrium (LA) Cardiac output (CO) and pulmonary mean transit time in seconds (MTT_P) were both calculated from the indicator time-concentration curve inscribed Pulmonary blood volume (PBV) was calculated as follows

$$PBV = (MTT_{PA\ to\ LA}) \times CO \quad (1)$$

In *Method II*[5] indicator was introduced into the pulmonary artery and left atrium in rapid succession and sampled from the femoral artery after both injections. Cardiac output was calculated from the pulmonary artery to femoral artery indicator time-concentration curve Pulmonary mean transit time is equal to the difference between the transit times from the pulmonary artery to the femoral artery and left atrium to femoral artery (FA) so that

$$PBV = (MTT_{PA\ to\ FA}) - (MTT_{LA\ to\ FA}) \times CO \quad (2)$$

In *Method III*[4] indicator was introduced into the superior vena cava (SVC) and sampled simultaneously from the pulmonary artery and left atrium Cardiac output was calculated from the superior vena cava to left atrium indicator time-concentration curve. Pulmonary mean transit time is equal to the difference between the transit times from the superior vena cava to the left atrium and superior vena cava to pulmonary artery so that

$$PBV = (MTT_{SVC\ to\ LA}) - (MTT_{SVC\ to\ PA}) \times CO \quad (3)$$

Cardiac output was also measured in each animal using the direct Fick method Accordingly expired air was collected in a Douglas bag for 10 minutes and samples of arterial and venous blood were obtained at the beginning and at the end of the 10-minute period The volume of the expired air was measured with a Tissot gasometer and the samples were analyzed for oxygen and carbon dioxide in duplicate by the Scholander method[7] The oxygen content of the samples of arterial and venous blood was determined in duplicate, utilizing the Roughton Scholander micromethod

All measurements of cardiac output and pulmonary blood volume were related to body weight.

Results

Cardiac output There were no consistent differences among the cardiac output values determined by the three indicator dilution methods (Fig 1) *Each of the* indicator-dilution methods tended to yield higher values for cardiac output than did the direct Fick method (Fig 2) However there was no statistically significant difference in cardiac output between the means of any of the methods regardless of how they were paired

Pulmonary mean transit time It can be seen from Fig 3 that the values for pulmonary mean transit time determined by

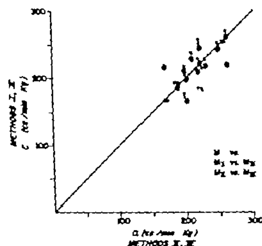


Fig. 1. Comparison of cardiac output values determined by the three indicator-dilution methods

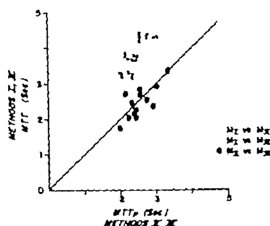


Fig. 3. Comparison of pulmonary mean transit times determined by the three indicator-dilution methods

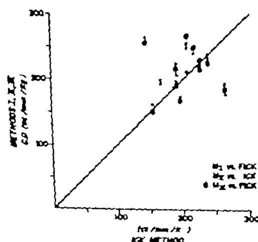


Fig. 2. Comparison of cardiac output values determined by the three indicator-dilution methods with that determined by the Fick method

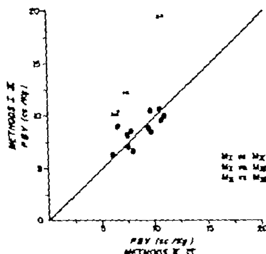


Fig. 4. Comparison of pulmonary blood volumes determined by the three indicator-dilution methods

Methods II and III are in close agreement. Method I yielded consistently higher values for pulmonary mean transit time than did Method II or Method III. The difference between the means of Methods II and III was not statistically significant, whereas the differences between the means of Methods I and II and Methods I and III were highly significant ($p < 0.001$).

Pulmonary blood volume. There was good agreement in pulmonary blood volumes between Methods II and III (Fig. 4). Method I produced consistently higher values for pulmonary blood volume than did either Method II or Method III (Fig. 4). The difference between the means of Methods II and III was not statistically significant, whereas the difference between the means of Methods I and II and Methods I and III were highly significant ($p < 0.001$).

Discussion

Each of the four methods utilized in this study yielded comparable determinations of cardiac output. However, Method I

produced consistently higher values for pulmonary mean transit time and pulmonary blood volume than did Method II or Method III. In addition, Method I resulted in much greater scatter in pulmonary mean transit time and pulmonary blood volume than did either Method II or Method III. For example, the standard error for the 15 determinations of pulmonary blood volume with Method I was ±0.84, whereas for Methods II and III the standard errors were ±0.48 and ±0.41, respectively.

The higher values of pulmonary blood volume for Method I as compared to those for Method II or Method III are obviously due to the longer mean transit times obtained with Method I. The prolonged mean transit times obtained with Method I were most likely due to the fact that the dye was injected into the pulmonary artery and did not traverse a mixing chamber before it was sampled. It is interesting that the mean transit time determined by Method III agreed well with that determined by Method II. In Method III the right ventricle is the mixing chamber, and in Method II the left ventricle is the mixing chamber. Thus, in so far as the present study is concerned, the right ventricle was as adequate as the left ventricle as a mixing chamber.

Pulmonary blood volume in dogs determined by direct bleed-out was found to be 8.0 ml. per kilogram. Thus, Methods II (mean 8.03 ml. per kilogram) and III (mean 8.71 ml. per kilogram) were in closer agreement with the direct bleed-out determinations than was Method I (mean 13.6 ml. per kilogram).

From these experiments it would appear that determinations of pulmonary blood volume by the indicator-dilution method are more accurate when dye is injected in rapid succession into the pulmonary artery and left atrium and sampled from the femoral artery (Method II) or when dye is injected into the superior vena cava and sampled simultaneously from the pulmonary artery and left atrium (Method III) than when dye is injected into the pulmonary artery *and sampled from the left* atrium (Method I). Method III has the advantage of requiring only a single injection of dye. This is particularly important in experiments which require rapid determinations of pulmonary blood volume.

Conclusion

Three indicator-dilution methods for determining cardiac output and pulmonary blood volume were compared in 15 dogs. Injection of dye into the pulmonary artery and sampling from the left atrium (Method I) yielded consistently longer pulmonary mean transit times and higher pulmonary blood volumes than did injection of dye into the pulmonary artery and left atrium with sampling from the femoral artery (Method II) or single injection of dye into the superior vena cava with simultaneous sampling from the pulmonary artery and left atrium (Method III). Although measurements of cardiac output determined by the three indicator-dilution methods as well as by the Fick principle were in good agreement, there was considerable scatter among the individual values in all methods.

REFERENCES

1. Stewart, G. N.: The pulmonary circulation time, quantity of blood in lungs and output of blood, Am. J. Physiol. 58:20, 1921.
2. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on circulation; further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions, Am. J. Physiol. 99:534, 1932.
3. Hyman, A. L., and Myers, W. S.: Hemodynamic changes following pulmonary embolization, Circulation 26:735, 1962.
4. Levinson, G. E., Frank, M. J., and Hellems, H. K.: The pulmonary vascular volume in man. Measurement from atrial dilution curves, Am. Heart J. 67:734, 1964.
5. Milnor, W. R., Jose, A. D., and McGaff, C. J.: Pulmonary vascular volume resistance and compliance in man, Circulation 22:130, 1960.
6. De Freitas, F. M., Faraco, E. Z., Nedel, N., De Azevedo, D. F., and Zaduchliver, J.: Determination of pulmonary blood volume by single intravenous injection of one indicator in patients with normal and high pulmonary vascular pressure, Circulation 30:370, 1964.
7. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J. Biol. Chem. 16:235, 1947.
8. Roughton, F. J. W., and Scholander, P. F.: Microgasometric estimation of the blood gases. I. Oxygen, J. Biol. Chem. 148:541, 1943.
9. Plumier, L.: La circulation pulmonaire chez le chien, Arch. Internat. Physiol. 1:176, 1904.

Hemodynamic responses to beta-adrenergic blockade in dogs

Yen Shen, M.D.
Antonio C. Quiroz, M.D.
George E. Burch, M.D.
Nicholas P. DePasquale, M.D.
New Orleans, La.

Inasmuch as heart rate, myocardial tension, and the velocity of myocardial contraction are important determinants of myocardial oxygen requirements, it is not surprising that clinicians were quick to apply the recently synthesized beta-receptor antagonists to patients with a variety of cardiac disorders. Thus far, beta-receptor antagonists have been reported to be beneficial in patients with angina pectoris,[1-3] myocardial infarction, arterial hypertension, muscular subaortic stenosis,[4] tetralogy of Fallot,[5] and cardiac arrhythmia.[6-8] Since the use of beta-receptor antagonists is being advocated in patients with serious heart disease, we considered it advisable to learn more about the systemic and pulmonary vascular responses to these compounds.

Material and methods

Five adult mongrel dogs weighing from 15.0 to 15.7 kilograms (average 15.3 kilograms) were lightly anesthetized with urethane (1.5 Gm. per kilogram) and loosely taped supine to a fluoroscopic table. After intubation with an endotracheal tube, 100 per cent oxygen mixed with room air was given at a rate of 2 to 2.5 L. per minute.

A yellow Kifa catheter was introduced from a jugular vein transseptally into a small pulmonary vein just proximal to the pulmonary vein wedge.[11] A second Kifa catheter was advanced into the left atrium. Catheters were also placed in the main pulmonary artery just beyond the pulmonic valve, in the right atrium at the orifice of the inferior vena cava, in the right femoral artery, in the right femoral vein, and in a small vein in the left hind paw. All catheters were connected by means of polyethylene tubing to Statham strain gauge transducers (P23Db), and mean pressures were recorded simultaneously by means of a multichannel oscillographic Electronics for Medicine recorder. Zero levels were determined to be 7 to 9 cm. from the top of the fluoroscopic table.

Cardiac output and pulmonary blood volume were measured by the d[illegible]e-dilution technique utilizing the method of Hamilton and associates.[illegible] A known quantity of indocyanine dye (Cardio-Green) was injected into the inferior vena cava, and blood was withd[illegible]wn simultaneously and

Supported by grants from the United States Public Health Service.
From the Department of Medicine, Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, La.
Received for publication June 29, 1964.
Address: Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La., 70112.

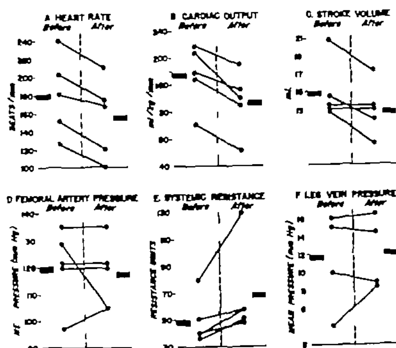


Fig. 1. Summary of systemic vascular responses to the rapid intravenous injection of 3 mg. of propranolol. The horizontal bars indicate the means.

at a constant rate through a matched pair of Gilford cuvette densitometers from catheters placed in the pulmonary artery and left atrium. Details of the method have been described by De Freitas and co-workers. Systemic and pulmonary vascular resistances were calculated using standard hemodynamic formulae.

After it had been determined that the animals were in a steady hemodynamic state, 3 mg. of propranolol in normal saline was rapidly injected intravenously. Pressures were monitored continuously and cardiac output and pulmonary blood volume were determined at the time of the maximum change in pressure, i.e., 10 to 15 minutes after injection of propranolol.

Results

The results are summarized in Figs. 1-3.

Systemic vascular responses. Intravenous injection of propranolol resulted in a decrease in heart rate (mean 14 per cent) and in cardiac output (mean 22 per cent) in all animals (Fig. 1). Stroke volume decreased in 3 dogs and did not change in 2 dogs (Fig. 1). The mean femoral arterial pressure remained unchanged in 3 dogs, increased slightly in 1 dog, and decreased in 1 dog. Systemic venous pressure, measured in 4 dogs, remained essentially unchanged in 3 and increased in 1 (Fig. 1). Total systemic vascular resistance increased in all animals (mean 42 per cent).

Pulmonary vascular responses. Intravenous injection of propranolol was followed by a decrease in mean pulmonary arterial pressure (mean 11 per cent) and a marked increase in left atrial pressure (mean 126 per cent) in all dogs (Fig. 2). Small pulmonary vein pressure, measured in 4 animals, remained essentially unchanged in 2 and increased slightly in 2 (Fig. 2). Pulmonary blood volume increased in 3 dogs, decreased slightly in 1 dog, and did not change in 1 dog (Fig. 2). Total pulmonary vascular resistance decreased in 2 dogs and increased slightly in 3 dogs (Fig. 2).

Fluoroscopic examination of the heart. Fluoroscopic examination of the heart indicated that at the time of the maximum pressure response the heart size had in-

*Supplied as Inderal by Ayerst Laboratories, Inc., New York, N.Y.

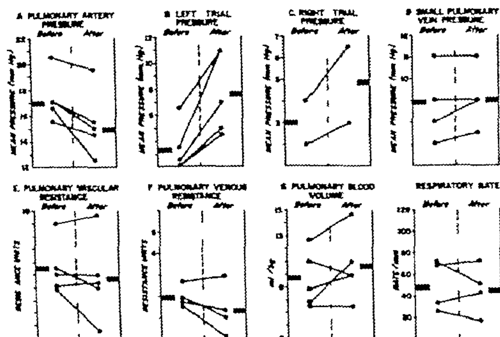


Fig 2 Summary of pulmonary vascular responses to the rapid intravenous injection of 3 mg. of propranolol. The horizontal bars indicate the means.



Fig. 3 Heart size before (*left*) and after (*right*) beta-adrenergic blockade

creased and ventricular contractility had decreased as compared to the control (Fig 3)

Discussion

Myocardial beta adrenergic receptors are at least in part responsible for the chronotropic and inotropic drive of the heart.[1] In the present study beta receptor blockade resulted in a decrease in heart rate and cardiac output and an increase in left atrial pressure. Heart size increased and myocardial contractility decreased. Decreased myocardial contractility after the administration of propranolol has been quantitated by others. Since

myocardial oxygen consumption is to a great extent determined by the rate at which myocardial tension is developed and the length of time that tension is maintained[18-22] it is probable that beta adrenergic blockade decreased myocardial oxygen requirements However this metabolic advantage occurs at the expense of an obvious mechanical disadvantage as indicated by the increase in left atrial pressure and heart size[22] Although the rate of development of myocardial tension decreased the absolute levels of tension produced by the myocardium must have increased since heart size increased with no change in arterial pressure The administration of propranolol also resulted in depressed ventricular function i.e. external stroke work decreased while left atrial pressure increased

Myocardial depression by means of beta adrenergic blockade has been shown to be beneficial in patients with angina pectoris and myocardial infarction. This effect is probably due to a decrease in myocardial oxygen requirements which appear to be directly related to the rate at which myocardial tension develops. However it would appear from the present study that beta-adrenergic blockade is potentially hazardous, particularly in patients with congestive heart failure Patients with congestive heart failure display increased sympathetic activity which at least in the early stages of heart failure is compensatory Removing the sympathetic drive of the heart may worsen the heart failure Furthermore increasing the mechanical disadvantage under which the heart is already functioning in patients with congestive heart failure may aggravate the failure.

Summary

Rapid intravenous injection of propranolol resulted in a decrease in heart rate and cardiac output and an increase in left atrial pressure in each of 5 dogs. Fluoroscopically heart size increased and myocardial contractility decreased Although the administration of propranolol decreases myocardial oxygen requirements, it also results in a mechanical disadvantage by increasing heart size It is suggested that beta adrenergic blockade may be hazardous in patients with low cardiac reserve.

REFERENCES

1 Dornhorst, A. C., and Robinson, B F Clinical pharmacology of a beta-adrenergic blocking agent, Lancet 2:312, 1962

2. Prichard, B. N C., Dickinson, C. J Alleyne, G A. O Hurst, P Hill, I D Rosenheim M L., and Laurence, D R. Effect of pronethalol in angina pectoris, Brit. M J 2 1226, 1963.

3 Hamer J Grandjean, T Melendez, L., and Sowton G E.: Effect of propranolol (Inderal) in angina pectoris preliminary report, Brit. M J 2 720, 1964

4 Srivastava, S C., Dewar H. A. and Newell, D J Double-blind trial of propranolol (Inderal) in angina of effort Brit M J 2 724 1964

5 Keelan P Double-blind trial of propranolol (Inderal) in angina pectoris, Brit. M J 1:897 1965

6. Snow P J D Effect of propranolol in myocardial infarction, Lancet 2:551 1965.

7 Prichard B N C. Hypotensive action of pronethalol Brit. M. J 1 1227 1964

8. Harrison, D C. Ross, J Glick, G., Chidsey C A., and Braunwald, E.: Hemodynamic effects of beta-adrenergic blockade in hypertrophic subaortic stenosis, Clin. Res. 11 167 1963.

9 Harrison, D C., Braunwald, E., Glick, G Mason, D T Chidsey C. A. and Ross, J: Effects of beta-adrenergic blockade on the circulation, with particular reference to observation in patients with hypertrophic subaortic stenosis, Circulation 29:84 1964

10. Cumming G R and Carr W: Relief of dyspnoeic attacks in Fallot tetralogy with propranolol, Lancet 1:519 1966.

11 Stock J P P and Dale, N Beta-adrenergic receptor blockade in cardiac arrhythmias, Brit. M J 2 1230 1963

12. Payne J P and Senfield R. M: Propranolol in the treatment of ventricular arrhythmia during anesthesia, Brit. M J 1:603, 1964.

13 Sloman, G Robinson J S and McClean, K. Propranolol in persistent ventricular fibrillation, Brit. M J 1:895 1964

14. Rowlands, D J Howitt, G and Markman, P Propranolol (Inderal) in disturbances of cardiac rhythm Brit. M J 1:891 1965.

15 DePasquale, N P Hyman, A. L and Burch, G. E.: Response of the pulmonary vein to rapid blood transfusion in intact dogs, J Lab. & Clin. Med. 65 122, 1965

16. Hamilton, W F Moore, J W Kinsman, J M and Spurling R. G.: Studies on circulation further analysis of injection method and of changes in hemodynamics under physiological and pathological conditions, Am. J Physiol 99:534 1932

17 De Freitas, F M Faraco, E. Z., Nedel, N De Azevedo, D F and Zaduchliver J Determination of pulmonary blood volume by single intravenous injection of one indicator

in patients with normal and high pulmonary vascular pressures, Circulation 30:370 1964.
18. Ahlquist R. P Study of adrenotropic receptor Am. J Physiol. 153:586, 1948
19. Folle, L. E., and A iado, D M Cardiovascular effects of anoxia and the influence of a new beta-adrenergic receptor blocking agent, J Pharmacol. & Exper Therap. 149 79 1965
20. Sarnoff S. J Braunwald, E., Welch, G. H., Case, R. B., Stainsby W N and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart, ith pecial reference to the time tension index, Am. J Physiol. 192 148, 1958.
21. Monroe, R. G. Myocardial oxyge consumption during ventricular contraction and e laxation, Circulation Res. 9:362, 1964
22. Sonnenblick, E. H., Ross, J Covell, J W Kaiser G A., and Braunwald, E. Velocity of contraction a determinant of myocardial oxygen consumption, Am J Physiol. 209:919 1965
23. Burch, G E., Ray C. T and Cronvich, J A. The George Fahr Lecture Certain mechanical peculiarities of the human cardiac pump in normal and diseased states, Circulation 5:504 1952.

Influence of mineralocorticoids and cations on the inotropic effect of angiotensin and norepinephrine in isolated cardiac muscle

Allan M. Lefer, Ph.D.
Charlottesville, Va.

Pretreatment with certain corticosteroids (e.g., mineralocorticoids) was found previously to potentiate the inotropic, pressor, and chronotropic effects of intravenously administered angiotensin and norepinephrine in the intact dog.[1] Concomitant with the potentiation was an elevated concentration of plasma sodium and a decreased concentration of plasma potassium. A high intake of dietary sodium duplicated the potentiation, whereas a low intake of sodium abolished the potentiation and caused a diminution in response. These facts suggested that the concentration of sodium in the myocardial extracellular fluid may play an important role in mediating the mineralocorticoid-induced potentiation to these agents. Such a mechanism has been proposed independently by Raab[2] and Ross. In addition, Tobian and Binion showed that desoxycorticosterone acetate (DOCA) caused an increase in the concentration of sodium in the arterial wall parallel with the induction of hypertension by this steroid.

The purposes of this study were to determine (1) whether aldosterone and DOC (desoxycorticosterone), which potentiated the inotropic effects of angiotensin and norepinephrine in vivo, could do so in vitro and (2) whether such a potentiation could be mediated by alteration of the concentrations of electrolytes, particularly sodium, in the bathing medium of isolated papillary muscles, wherein the concentration can be precisely controlled.

Methods

Fifty-three cats of either sex weighing between 1.4 and 3.4 kilograms were used in this study. The cats were preanesthetized with ether and then further anesthetized to a surgical plane with intravenously administered pentobarbital sodium (20 mg. per kilogram). Cardiectomy was rapidly performed under positive-pressure respiration. Two papillary muscles were dissected from the right ventricle of each heart in oxygenated Krebs-Henseleit solution at room temperature and immediately mounted in 20-ml., water-jacketed chambers maintained at 37±0.1°C. The composition of the modified Krebs-Henseleit buffer has been previously described. The pH of this solution is 7.3 after equilibration with 95 per cent O_2 and 5 per cent CO_2, and the osmolality is 28? mOsm.

From the Department of Physiology, University of Virginia School of Medicine, Charlottesville, Va.
Supported by Grant No. HE-09921 from the National Heart Institute of the National Institutes of Health.
Part of this work was presented at the Federation of American Societies for Experimental Biology Meetings on April 12, 1966, in Atlantic City, N. J.
Received for publication June 30, 1966.

It was found that cat papillary muscles function at a very stable level of contractility for 4 to 6 hours in this solution.

Each papillary muscle was electrically stimulated with two platinum field electrodes mechanically fixed 1 cm. apart in the bath. Rectangular wave pulses of threshold plus 2 volt strength (threshold usually about 0.5 to 1.0 volt), 16.7 msec. duration, and a frequency of 1 per second were used. An active length tension relationship was individually determined for each muscle. The resting tension was then set at a level just below that which yielded maximum developed tension. Under these conditions, muscles exhibited developed tensions of about 1.5 grams per square millimeter of cross-sectional area. Isometric contractions of the electrically driven papillary muscles were measured by Grass FT-03 force-displacement transducers and continuously recorded on a Beckman-Offner Type RB Dynograph.

The following drugs and hormones were freshly prepared for each experiment and diluted in Krebs-Henseleit buffer: d-aldosterone (Ciba) dissolved in 95 per cent ethanol, desoxycorticosterone (Calbiochem Grade A), crystalline synthetic angiotensin amide (Hypertensin, Ciba) prepared from lyophilized powder, and norepinephrine bitartrate (Levophed, Sterling Winthrop). Concentrations of angiotensin and norepinephrine were calculated as the free base. Appropriate concentrations of ethanol were alternated in a sequence with administrations of steroid. A double cross-over design was used to eliminate variations in responsiveness between a given pair of papillary muscles. Volumes of drug solution added to the bath were between 0.1 and 0.5 ml. Reserpinization of cats was accomplished by injecting 1.0 mg. per kilogram of reserpine (Serpasil, Ciba) intraperitoneally on the first day and 0.5 mg. per kilogram for the next 2 days. These cats were used as experimental subjects on the fourth day and were paired with cats given the same volumes of the reserpine vehicle.

Statistical significance was evaluated using Student's "t" test.

Results

A concentration response curve of the positive inotropic effect of angiotensin was

Table I. Influence of mineralocorticoids on the positive inotropic effect of angiotensin II (5×10 [illegible] M) in vitro

Bathing medium	Pretreatment with		Per cent increase in contractile force		Number of muscles
	Hormone	Concentration	Response to angiotensin after hormone	Response to angiotensin after vehicle‡	
Normal Krebs-Henseleit buffer (2.54 mM calcium)	DOC*	1×10[illegible] M	56.4 ± 7.9	53.3 ± 6.4	6
		1×10[illegible] M	43.8 ± 8.1	56.1 ± 4.9	6
	Aldo†	1×10[illegible] M	51.2 ± 5.0	46.4 ± 6	
		1×10[illegible] M	49.8 ± 4.7	48.5 ± 5.9	6
Low calcium Krebs-Henseleit (0.63 mM calcium)	DOC	1×10[illegible] M	56.3 ± 8.6	66.6 ± 11.0	10
		1×10[illegible] M	53.1 ± 5	56.1 ± 9.1	10
		1×10[illegible] M	61.4 ± 7.8	59.3 ±	10
		5×10[illegible] M	60.0 ± 6.7	66.5 ± 10.6	8
	Aldo	1×10[illegible] M	70.9 ± 6.4	0 ± 6.5	4
		1×10[illegible] M	66.6 ± 9.4	69.5 ± 7.4	1
		1×10[illegible] M	68 ±	6 0 ± 6.1	1

All values are mean increases in contractile force expressed as per cent increase.
*Desoxycorticosterone.
†Aldosterone.
‡Vehicle: Equal volumes of 95 per cent ethanol.

determined Reproducible effects of a suitable magnitude were obtained at a concentration of 5×10 M This point lies near the peak of the linear portion of the concentration response curve Table I summarizes the results of administration of DOC and aldosterone to the bath 30 minutes prior to the angiotensin Altering this time between administration of the drugs to 60 minutes had no demonstrable difference on the angiotensin response. It can be clearly seen that DOC and aldosterone had no modifying influence on the magnitude of the angiotensin induced positive inotropic effect when compared to the corresponding effect of angiotensin after the administration of ethanol This same lack of potentiation occurred in both the normal Krebs-Henseleit and in the low-calcium buffer No significant differences in the magnitude of the angiotensin induced inotropic response in low-calcium buffer occurred when compared to the responses to normal buffer Aldosterone and DOC also failed to potentiate the inotropic effect of norepinephrine in the cat papillary muscle preparation. Table II summarizes these data. Comparing the steroid pretreatment with ethanol (vehicle) no significant potentiation of the norepinephrine induced inotropic effect occurred in either normal or low-calcium buffer However in contrast to results with angiotensin the effect of norepinephrine per se in the low-calcium medium was greater than in the normal-calcium medium The norepinephrine response in the low-calcium medium is about twice that seen in the normal-calcium medium This difference is statistically significant ($p < 0\ 001$)

An attempt was made to ascertain whether the corticosteroid potentiation of the inotropic effect of angiotensin seen in vivo could be duplicated in vitro by altering the concentrations of sodium and potassium in the bathing medium Elevation of the concentration of sodium from 130 to 160 mM lowered the developed tension of the papillary muscles by about 25 per cent, whereas reduction of the concentration of sodium from 130 to 100 mM increased developed tension by about 25 per cent. These effects reached equilibrium in about 15 minutes. Corticosteroids, administered soon after this equilibrium was reached exerted negligible inotropic effects over the 30-minute test period Angiotensin effects reached a peak within 2 to 4 minutes after addition to the bath

Table II Influence of mineralocorticoids on the positive inotropic effect of norepinephrine (4×10^{-8}M) in vitro

Bathing medium	*Pretreatment with*		*Per cent increase in contractile force*		*Number of muscles*
	Hormone	*Concentration*	*Response to norepinephrine after hormone*	*Response to norepinephrine after vehicle* ‡	
Normal Krebs-Henseleit buffer (2 54 mM calcium)	DOC*	1×10^{-7}M	51 8 ± 8 4	55 3 ± 7 9	6
		1×10^{-6}M	51 0 ± 5 6	52 7 ± 6 4	6
	Aldo†	1×10 M	53 7 ± 7 2	54 4 ± 6 8	8
		1×10^{-6}M	50 1 ± 6 1	48 2 ± 6 2	8
Low calcium Krebs-Henseleit buffer (0 63 mM calcium)	DOC	1×10^{-7}M	105 2 ± 7 4	106 5 ± 8 2	6
		1×10 M	99 3 ± 8 1	97 7 ± 7 3	6
	Aldo	1×10^{-7}M	101 4 ± 7 1	110 1 ± 10 9	7
		1×10^{-6}M	103 5 ± 16 3	99 2 ± 14 0	6

All values are mean increases in contractile force expressed as per cent increase ± S E M

*Deoxycorticosterone

†Aldosterone

‡Vehicle = Equal volumes of 95 per cent ethanol.

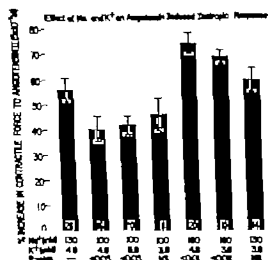


Fig. 1. Effect of alterations in the external sodium and potassium on the positive inotropic response to angiotensin. The height of each bar represents the mean per cent increase in contractile force to 5X10 angiotensin. Standard errors of the mean are indicated by the T-bars. The number of muscles used is shown at the bottom of the bars. The concentrations of sodium and potassium in the external medium bathing the muscles, in millimoles per liter, are shown under the bars. The values of the bars are all compared to that shown in the first bar (130 mM Na, and 4.8 mM K). P values are given for those cases in which values are significantly different from this reference value.

as compared to 1 to 2 minutes for the peak of the norepinephrine effect. Fig. 1 is a bar graph summarizing the data in this part of the study. Significant decreases in the angiotensin-induced inotropic response occurred when the papillary muscles were bathed in a low sodium (100 mM) medium regardless of whether the concentration of potassium was normal or elevated. When both the concentration of sodium and that of potassium were lowered (*fourth bar*) there was no significant reduction in inotropic response probably because of greater variability as evidenced by the higher standard errors. Conversely when the concentration of sodium was elevated to 160 mM in the presence of either normal or reduced concentrations of potassium the inotropic response to angiotensin (5×10^{-7}) was significantly enhanced. Simply reducing the concentration of potassium to 3.8 mM in the presence of a normal concentration of sodium had no modifying influence on the inotropic response to angiotensin. These data show that it is the elevated concentration of sodium rather than the decreased concentration of potassium that correlates best with the mineralocorticoid potentiation of the angiotensin induced inotropic response. Since these are the two major cations influenced by corticosteroids this constitutes strong suggestive evidence that the mineralocorticoid potentiation of angiotensin seen in vivo is in some way mediated by an increased concentration of sodium in the extracellular fluid and or tissue.

The situation is different with regard to the effect of sodium ions on the inotropic response to norepinephrine. Table III summarizes these results. It is clear that alteration of the concentration of sodium ions within the same range as that used for angiotensin had no modifying influence on the positive inotropic response to norepinephrine ($4 \times 10^{-}$ M). No modifying effect occurred when the osmolality was increased. These findings are in direct contrast to those obtained when angiotensin was used even though both agents were potentiated by DOCA in vivo.

Finally the effects of depletion of tissue catecholamines on the positive inotropic response to angiotensin was determined using whole animal reserpinization to deplete myocardial levels of catecholamines. This protocol is within the dose range which effectively depletes the levels of catecholamines in cardiac tissue to less than 2 per cent of control values. Fig. 2 shows that reserpinization had no influence on the inotropic response to angiotensin in normal Krebs-Henseleit buffer when compared to that of reserpine vehicle treated cats (*left panel*). Furthermore reserpine did not abolish the potentiation of the inotropic response to angiotensin normally seen in the high-sodium medium.

Discussion

No previously published data are available on the modifying influence of mineralocorticoids on the inotropic effect of angiotensin and norepinephrine in vitro. The data obtained in this study indicate that aldosterone and DOC do not potentiate either of these inotropic agents at the

Table III. Effect of altering the external sodium concentration on the positive inotropic effect of norepinephrine (4×10 M) in vitro

Sodium concentration (mM)	Sucrose (60 mM)	Osmolality (mOsm)	Per cent increase in contractile force in response to norepinephrine* (4×10⁻⁸M)	Number of muscles
130	−	282	59.0 ± 7.3	9
100	−	241		9
100	+	281	50.2 ± 7.8	9
130	+	322	55.8 ± 5.8	7
160	−	326	50.7 ± 7.2	9

All values are mean increases in contractile force expressed as per cent increase ± S.E.M.
Muscles do not contract very long in this medium.

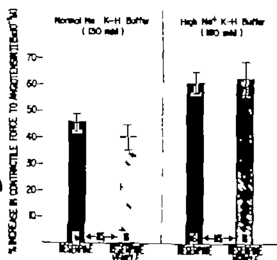


Fig. Effect of reserpine on the positive inotropic response to 5×10 angiotensin. Bars indicate mean values ± S.E.M. Numbers shown at the bottom of the bars are the number of muscles used, duplicate runs being made in all muscles. Reserpine did not significantly alter the inotropic response to angiotensin in either the normal-sodium buffer (130 mM) or in the elevated-sodium buffer (160 mM).

concentrations used in isolated cat papillary muscles. It is possible that these mineralocorticoids would potentiate low concentrations of angiotensin and norepinephrine. This implies but does not prove that the corticosteroid potentiation seen in vivo is not via a direct action on the myocardium. It is possible that mineralocorticoids would potentiate if administered for times longer than 1 hour. However, these mineralocorticoids were effective in antagonizing the positive inotropic effect of ouabain under the same conditions within 30 minutes.[6]

Other investigators have found that a variety of corticosteroids potentiate the catecholamine-induced contractions of isolated strips of vascular smooth muscle. Fowler and Chou[7] showed that both glucocorticoids and mineralocorticoids potentiated the contractile effects of norepinephrine in rabbit aortic strips. Others have shown that DOC, aldosterone, 2α methyl 9α fluorocortisol, cortisol, and cortisone potentiate the epinephrine-induced contractions of isolated rabbit aortic strips.[8-11] However, Sparks[12] could not obtain potentiation of angiotensin under very similar conditions using the same preparation. Therefore, cardiac and vascular smooth muscle behave similarly with regard to lack of potentiation of angiotensin effects. However, vascular smooth muscle appears to be capable of potentiation by corticosteroids to catecholamines, whereas cardiac muscle is not potentiated under these conditions. Perhaps this difference between these two tissues is due to a different distribution of adrenergic receptors in these tissues.

The cat papillary muscle exhibited changes in developed tension when placed in solutions containing altered concentrations of sodium or calcium. Cardiac muscle is known to be sensitive to changes in concentration of cations in the external medium. Contractility of cardiac muscle

varies directly with the concentration of calcium ions and inversely with the concentration of sodium ions. Developed tension is thus proportional to $[Ca^{++}]/[Na^{+}]^2$ in cardiac muscle.[11, 1] The results obtained in this study in general agree with these findings. Furthermore alteration in the concentration of sodium and calcium modified the inotropic response to angiotensin and norepinephrine. The data in Tables I and II clearly show that the inotropic response to norepinephrine but not to angiotensin is enhanced in the low-calcium medium. However mineralocorticoids did not potentiate angiotensin or norepinephrine in the low-calcium medium even though these steroids exert greater inotropic effects under these conditions.[13] Thus, the concentration of calcium in the external medium seems to have little modifying effect on the capacity of corticosteroids to potentiate the inotropic effect of angiotensin and norepinephrine.

The concentration of sodium in the external medium was altered to determine whether increasing the concentration of sodium ions could duplicate the potentiation seen with DOCA and with an elevated intake of sodium in vivo. Elevating the concentration of sodium ions in vitro did enhance the angiotensin response but not the norepinephrine response.[10] Koch Weser[17] found similar inotropic responses to angiotensin with comparable changes in the concentration of sodium. However conflicting reports exist with regard to smooth muscle. Khairallah and associates[1] found that decreasing the concentration of sodium ions in the medium diminished the contractile response of the isolated guinea pig ileum and rat uterus to angiotensin. However Napodano and associates[1] reported that decreasing by 25 per cent the concentration of sodium in the medium bathing rabbit aortic strips enhanced the responsiveness of these strips to angiotensin. It is not possible at this time to resolve these apparently divergent findings but this difference may be due to the fact that activation of α and β adrenergic receptors in the intestine causes relaxation of smooth muscle, whereas activation of α receptors in vascular smooth muscle results in contraction. The failure of an elevated concentration of sodium ions to enhance the inotropic effect of norepinephrine also confirms the work of Reiter and Schober[18] in guinea pig papillary muscles.

In the present study it appears that it is the elevated concentration of sodium ions per se and not merely an increased osmolarity of the medium which increases the responsiveness of the papillary muscles to angiotensin because adding sucrose to the medium as a substitute for sodium did not cause the potentiation.

The physiologic significance of the potentiation of the cardiac effects of angiotensin by an elevated concentration of sodium ions in the extracellular fluid is not clear. Presumably elevating the concentration of plasma sodium inhibits the release of angiotensin thereby decreasing the secretion of aldosterone.[19] At the same time an elevated level of sodium potentiates the positive inotropic and pressor effects of angiotensin thus enhancing the sodium retaining effect of the circulating aldosterone.

Summary

Both aldosterone and desoxycorticosterone (DOC) over a relatively wide range of concentrations failed to potentiate the positive inotropic effect of angiotensin and of norepinephrine in the isolated cat papillary muscle. Lowering the concentration of calcium in the bathing *medium* did not alter this relationship. Lowering the concentration of sodium in the medium itself reduced the inotropic responsiveness of the isolated cardiac muscle to 5×10 M angiotensin. Raising the concentration of sodium enhanced the positive inotropic effect of angiotensin. This enhancement seen to be independent of changes [illegible] of the solution. Altering th[illegible] concentration of potassium did not [illegible] any [illegible] influence on th[illegible] angiotensin response. Prior reserpin[illegible] of the [illegible] did not alter the inotropic response to angiotensin nor did it bl[illegible] the enhanced effect seen in the presence of an elevated level of sodium. Therefore the enhancement probably does not depend on the release of catecholamines stored in cardiac tissue. Altering the concentration of sodium in the medium did not modify the positive inotropic response to 4×10 M norepinephrine.

The findings in this study do not completely account for the mechanism of potentiation of angiotensin by mineralocorticoids reported in vivo. However, they strongly suggest that the potentiation of the cardiac effects of angiotensin seen in the intact dog is mediated by the sodium retaining effects of these hormones in vivo.

The technical assistance of Mr. Thomas F. Inge, Jr., is gratefully acknowledged. I also wish to thank Dr. J. J. Chart, Ciba Pharmaceutical Corporation, Summit, N. J., for a generous supply of synthetic angiotensin amide (Hypertensin, Ciba).

REFERENCES

1. Lefer, A. M., Manwaring, J. L., and Verrier, R. L.: Effect of corticosteroids on the cardiovascular responses to angiotensin and norepinephrine, J. Pharmacol. & Exper. Therap. 154:83, 1966.
2. Raab, W.: Transmembrane cationic gradient and blood pressure regulation, Am. J. Cardiol. 1:752, 1959.
3. Ross, E. J.: The adrenal medulla, the adrenal cortex, sodium and blood pressure, Proc. Roy. Soc. Med. 51:1005, 1959.
4. Tobian, L., and Binion, J.: Artery wall electrolytes in renal and DCA hypertension, J. Clin. Invest. 33:1407, 1954.
5. Tanz, R. D.: The action of ouabain on cardiac muscle treated with reserpine and dichloroisoproterenol, J. Pharmacol. & Exper. Therap. 144:205, 1964.
6. Lefer, A. M.: Corticosteroid antagonism of the positive inotropic effect of ouabain, J. Pharmacol. & Exper. Therap. 151:294, 1966.
7. Fowler, N. O., and Chou, N. H. F.: Potentiation of smooth muscle contraction by adrenal steroids, Circulation Res. 9:153, 1961.
8. Rondell, P., and Gross, F.: Method for isometric recording from isolated vessels under various conditions, Helvet. Physiol. Pharmacol. Acta 18:366, 1960.
9. Heineman, A. C., Jr., and Danowski, T. S.: Potentiation and stabilization of aortic strip pressor assay by plasma and hydrocortisone: Routine use in the diagnosis of pheochromocytoma, Am. J. M. Sc. 239:167, 1960.
10. Bohr, D. F., Brodie, D. C., and Cheu, D. H.: Effect of electrolytes on arterial muscle contraction, Circulation 17:746, 1958.
11. Bohr, D. F.: Electrolytes and corticosteroids in relation to vascular reactivity, Proc. Cardiology Congress (Mexico City) 4A:253, 1962.
12. Sparks, H. V.: Effects of angiotensin and desoxycorticosterol on isolated arteries and veins, Univ. Michigan Med. Bull. 29:243, 1963.
13. Luttgau, H. C., and Niedergerke, R.: The antagonism between Ca and Na ions on the frog heart, J. Physiol. (London) 143:486, 1958.
14. Leonard, E., and Hajdu, S.: Action of electrolytes and drugs on the contractile mechanism of the cardiac muscle cell, Handbook of physiology, Sec. 2, Circulation, Vol. 1, p. 151, Baltimore, 1962, Williams & Wilkins.
15. Lefer, A. M., and Sayers, G.: Antagonism of the inotropic action of ouabain by aldosterone, Am. J. Physiol. 208:649, 1965.
16. Reiter, M., and Schober, H. G.: Die positive inotrope Adrenalinwirkung auf den Meerschweinchen-Papillarmuskel bei Variation der äusseren Calcium- und Natriumkonzentration, Arch. exper. Path. Pharmakol. 250:9, 1965.
17. Koch-Weser, J.: Nature of the inotropic action of angiotensin on ventricular myocardium, Circulation Res. 16:230, 1965.
18. Khairallah, P. A., Vadaparampil, G. J., and Page, I. H.: Effect of ions on angiotensin interaction with smooth muscle, Arch. Int. Pharmacodyn. 158:155, 1965.
19. Napodano, R. J., Caliva, F. S., Lyons, C., DeSimone, J., and Lyons, R. H.: The reactivity to angiotensin of rabbit aorta strips after either alterations of external sodium environment or direct addition of benzydroflumethiazide, Am. Heart J. 64:498, 1962.
20. Blair-West, J. R., Coghlan, J. P., Denton, D. A., Goding, J. R., Wintour, M., and Wright, R. D.: Effect of variations of plasma sodium concentration on the adrenal response to angiotensin II, Circulation Res. 17:386, 1965.

Case reports

Paroxysmal atrial tachycardia associated with ECHO 9 virus infection

James D Cherry M.D
*Charles L. John M.D***
*Thomas C Meyer M D****
Madison Wis

Paroxysmal atrial tachycardia is a relatively uncommon cardiac illness of childhood with the majority of cases having their onset during the first 4½ months of life. The illness is frequently associated with congenital heart disease and the Wolff Parkinson White syndrome. In children without pre-existing heart disease etiological relationships are obscure although many cases occur in conjunction with mild ill-defined infections. The present study reports on a child with paroxysmal atrial tachycardia and virologic and serologic evidence of ECHO 9 virus infection. The virologic methods have been described elsewhere

Case report

J H 7-week-old boy was admitted to the hospital for the second time on Aug 31 1964 The patient had been previously hospitalized 16 days before because of pneumonia and bilateral pleuritis. On this first hospital admission the child was noted to have cardiac rate of 160 to 280 and an enlarging liver. In addition to antibiotic therapy digoxin was administered for 4 days because it was thought that the child might be experiencing early cardiac failure as result of his respiratory disease. No electrocardiogram was obtained The patient made rapid recovery and enjoyed good health until 6 hours prior to the second hospital admission at which time he was anorexic and tachypneic During the ensuing 6 hours he became pale cold, and lethargic On admission physical examination revealed pale irritable infant with respiratory rate of 30 and tachycardia of 280. Evaluation of the chest revealed only subcostal retractions There were no cardiac murmurs and the liver was not enlarged An electrocardiogram revealed paroxysmal atrial tachycardia (Fig 1) serial electrocardiograms are shown in Figs. 1 to 6.

Hematologic studies at the time of admission revealed white blood cell count of 8,200 cells per cubic millimeter with 29 per cent segmented neutrophils, 3 per cent band forms, 57 per cent lymphocytes, 8 per cent monocytes, and 1 per cent eosinophils. The hemoglobin was 8.6 Gm per cent and the hematocrit was 25 per cent Urinalysis was unremarkable and chest x-ray film was normal

The patient was digitalized with intramuscular deslanoside over 12-hour period (total dose of .07 mg per kilogram) and then placed on maintenance regimen of 0.1 mg of digoxin per day orally Within 12 hours of admission the cardiac rate had slowed considerably but electrocardiographic evidence of abnormality continued throughout the child's hospitalization (Figs 2 and 3)

On the fourth hospital day the child developed

From the John A. Hartford Research Laboratory Madison General Hospital St Marys Hospital and the Department of Pediatrics, University of Wisconsin School of Medicine Madison, Wis
Supported in part by United States Public Health Service Training Grant TI AI 37-01 Dr John and the John A. Hartford Foundation, Inc.
Received for publication June 17 1966
*Assistant Professor of Pediatrics, University of Wisconsin School of Medicine Director John A. Hartford Research Laboratory Markle Scholar in Academic Medicine Address Department of Pediatrics, University of Wisconsin School of Medicine 300 University Ave Madison, Wis 53706.
**Postdoctoral Research Fellow Department of Pediatrics, University of Wisconsin School of Medicine
***Assistant Professor of Pediatrics, and Assistant Dean, University of Wisconsin School of Medicine

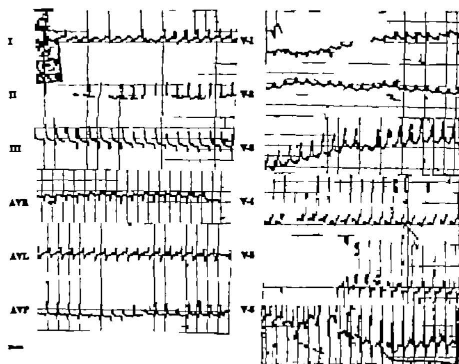


Fig 1 Tra ing of Aug 31 1964 bows a rate of 290 P R i terval of less tha 0 10 second nd small Q i Leads III nd AVF There is S-T depression in Leads I AVL nd V_4-V_6, with reciprocal elevation of S-T segments Leads AVR nd V The T w ve inverted in Leads I AVL V_4-V nd probably V The tracing show pra entricular tachycardia nd posterolateral wall ischemia

temperat re of 107°F Ph sical examin tion re ealed onl thick whit mucou nasal discharge. Throat and nasal bacterial cultures grew their respectiv normal floras chest x-ray film was w thi normal limits nd th white blood count w 8,500 cells per cubic millimeter with 52 per cent segmented neutrophils, 3 per cent band forms 43 per cent lymphocytes nd 2 per cent monocytes. The hemoglobin and hematocrit were 9 Gm. per cent nd 29 per cent, respectively and the erythrocyt sedimentation rate was 52 mm. per hour Th serum gl tamic oxalacetic transaminase was 82, nd the serum glutamic pyruvic transaminase was 34. Withi 24 hours the patient was agai afebrile nd the remainder of his hospital tay was unevent ful. He was discharged on Sept 10 1964 At this time repeat wh t blood count revealed 13 900 cells per cubic millimeter with 7 per cent segmented neutrophils, 87 per cent lymphocytes and 6 per cent monocytes The serum glutamic oxalacetic tran aminase was 66 and the serum glutamic pyruvic tra saminase was 57

After discharge the child experienced no dif ficulties except for two episodes of acut ot tis media His growth nd development for the first 12 months of lif had been within normal limits. Digoxin w discontinued on J ly 19 1965

ECHO 9 irus was isol ted from throat nd rectal wabs In pproximat conce trations of 128,000 and 40 tissue culture infectious doses (ID_{50}) per respectiv swab. A serum neutralizing antibody titer rise of < 10 t 40 t ECHO 9 irus was demonstrated.

Discussion

Simple paroxysmal atrial tachycardia is an uncommon but not rare, illness of childhood It is unique that the majority of pediatric cases occur in children who are less than 4½ months of age and of the cases without adequate evidence of etiology the preponderance is in boys.[1] Although the majority of cases cannot adequately be explained etiologically the history often reveals that the onset was associated with mild illness of the upper respiratory tract.

The series of electrocardiograms (Figs 1 to 6) are similar to those seen in cases of supraventricular tachycardia. The appearance of the very marked Q wave in the standard leads, and the persistence of S-T segment changes in the precordial leads without the child being on digitalis (Fig 6) raise the question of some ischemic change which has persisted The alternative is that there was actual necrosi of

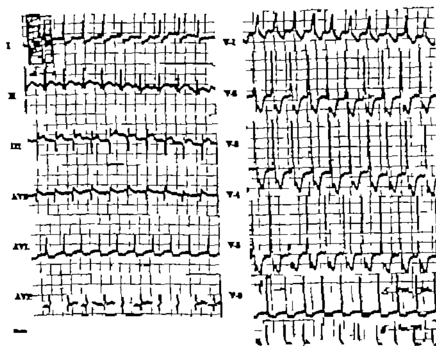


Fig. 2. The electrocardiogram taken 24 hours after admission, after digitalization. The rat has lowed to 150 and the Q wav has become significantly deeper in Leads III and AVF. There is further S-T change and there is general increase in oltage in the precordial leads. There is broad slurred R Lead V and the tracing hows digitalis effect.



Fig. 3. The t acing taken on the fourth da of illness. This show some decrease i digitalis effect, nd the T w is now normal in Lead I and V. The Q wav remains unchanged.

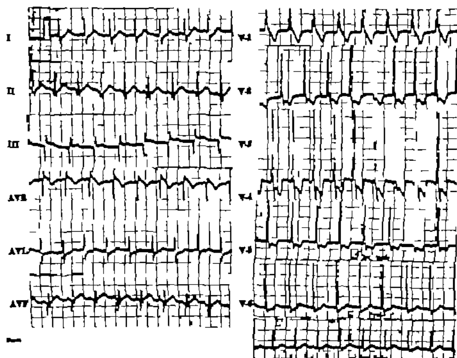


Fig. 4. The tracing obtained on the eleventh hospital day shows less general S-T deviation. This pattern persisted without much alteration for the next 6 months except that there was some improvement in the left chest lead.

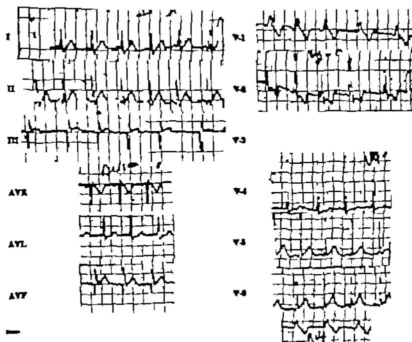


Fig. 5. The electrocardiogram obtained 9 months after the acute illness and while the patient still on digitalis. The rate is approximately 100 with P R of 0.12 second and QRS of 0.07 second. The Q w e persist in Leads III and AVF and the S-T segments remain depressed in Leads V and V

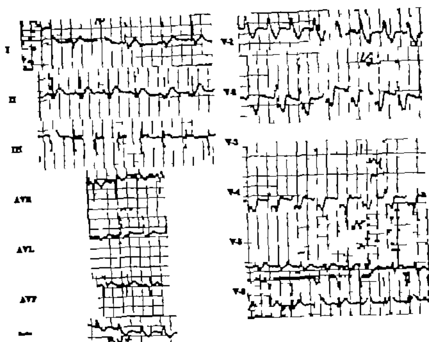


Fig 6 The tracing obtained 3 months after digitalis was discontinued (15 months after onset of illness). The rate varies between 80 and 120 per minute, and the P R interval remains at 0.12 second. Some further S-T depression in Leads AVL, V V4, and V is noted, but otherwise the tracing remains essentially similar to that obtained while the patient was on digitalis.

cardiac muscle caused by a myocarditis during the acute phase of the illness. The transaminase values and elevated sedimentation rate lend some support to both of these alternatives.

The pediatrician tends to discount a Q wave in Standard Lead III and Lead AVF However at its greatest (Fig 3) this Q wave is 1 1 millivolts in Lead III and apart from the initial tracing (Fig 1) it remains approximately 0.8 millivolt, which is the upper limit of normal in those tracings studied by Ziegler The Q wave in Lead AVF remains within the upper range of normal

Dominguez and associates[1] are persuasive in their argument that a viral myocarditis in children may closely resemble recent myocardial infarction electrocardiographically They cite 2 cases having sufficient similarity to this child's presentation in which autopsy revealed extensive necrosis with pleomorphic cellular exudate throughout the myocardium In one case the heart was normal in size and although they do not specify the mode of death of the child

it is conceivable that there was complete interruption of the conduction system and cardiac arrest at such an early stage in the disease that cardiac enlargement had not occurred We were unable to document cardiac enlargement at any stage in our patient.

It is difficult to explain the tachycardia noted at the time of the child first hospital admission when neither electrocardiograms nor viral studies were obtained. It seems to be probable, however that the increased cardiac rate was sinus in nature resulting from both fever and respiratory distress. On the other hand the tachycardia could have been an episode of paroxysmal supraventricular tachycardia. If this latter was the case, then the ECHO 9 virus infection probably could not be considered to be the primary causative factor of the tachycardia at the time of the second admission

The relation of Coxsackie B viruses to severe neonatal cardiac disease is well known.[6-10] It is of interest that many children with Coxsackie n y

Table I. Levels of plasma lipids in a patient with familial hypercholesterolemic xanthomatosis and in her family

	Cholesterol (mg./100 ml.)	Triglyceride (mg./100 ml.)	Phospholipid (mg./100 ml.)
Patient	503, 577	41	224
Living sister	375	—	—
Father	385	55	295
Mother	270	71	238
Normal values*	Under 250	30–130	Under 280

*Normal values in the laboratory of Dr. Norton Spritz, through whose courtesy these determinations were made, except for the level of cholesterol of the living sister, which was determined by a commercial laboratory in Liberty, N.Y.

stop work as a typist. Her physician noted an irregular heart rhythm, for which she was digitalized. The dyspnea persisted and was followed during the next 6 months by orthopnea, precordial distress, and paroxysmal nocturnal dyspnea. An electrocardiogram showed marked changes in S-T segments and T waves when compared with a 1961 tracing. In February 1965, she was admitted to a local hospital. She was afebrile with a pulse rate of 80 to 88 while at rest, and of 120 after mild exercise. Another electrocardiogram on March 10, 1965, was essentially unchanged. Because of her progressive dyspnea, she was transferred to the New York Hospital on March 12.

Family history. The parents are not related. The father was well at age 54 except for moderate hypertension. The mother, age 52, was obese and had a ventral hernia. The paternal grandmother had xanthelasma and "liver disorder." A younger sister of the patient had xanthomas in the finger webs and over the knees and elbows, confirmed by biopsy when she was 5 years old. A systolic heart murmur and an elevated sedimentation rate had been noted when she was 8 years old. A year later she had an elevated sedimentation rate, C-reactive protein, and antistreptolysin-O titer; an electrocardiogram showed sinus tachycardia at a rate of 140 with a pattern of questionable right ventricular hypertrophy and normal P-R interval. She died suddenly in 1961 at 11 years of age; death was ascribed to rheumatic fever. An older sister who was living and well at age 20 also has xanthomas and elevated plasma cholesterol. Determinations of plasma lipid in the members of this family are shown in Table I.

Physical examination. The temperature was 38.8° C., the pulse was 120 and regular, respirations were 16, and the blood pressure was 120/70 mm. Hg in the right arm and 115/60 mm. Hg in the left arm. The skin was warm and moist, with raised, soft, yellow-orange, nontender plaques in the finger webs of both hands. Similar plaques were present in both popliteal fossae. Nodular, firm, yellow subcutaneous lesions were also noted over the elbows and knees. Good popliteal and dorsalis pedis pulses were felt. There was no dependent edema. Corneal arcus was present in both eyes. The lungs were clear. The heart was not enlarged. A systolic thrust was felt in the midclavicular line in the fifth left intercostal space. A systolic thrill was felt over the base of the heart and over both carotid arteries. A harsh, rough, Grade 3/6 systolic murmur was heard over the whole precordium but was loudest over the aortic area and corresponded in time to the thrill. This murmur was well transmitted into both carotid arteries and the apex. No other murmurs were heard, nor was there gallop rhythm. The second sound was soft in quality. The liver and spleen were not felt.

Laboratory findings. Urinalysis was normal, except for a trace of protein in one specimen. Urine cultures showed a bacterial count greater than 10^5 with many *Aerobacter aerogenes* and *Escherichia coli* and few enterococci. The blood hematocrit, hemoglobin, white cell count, prothrombin time, electrolytes, urea nitrogen, uric acid, glucose, plasma proteins, glutamic oxaloacetic transaminase, and lactic dehydrogenase were within normal limits. Levels of total blood cholesterol were 503 and 577 mg. per 100 ml. on two occasions. Repeated blood cultures yielded no growth. Serum iron was 81 μg. and total iron-binding capacity 388 μg. per 100 ml. Direct and indirect Coombs tests were negative, and the haptoglobin level was normal. Blood Wassermann reactions and lupus erythematosus cell preparations were also negative. Widal, Weil-Felix, heterophil, and Brucella agglutination tests were negative. Protein-bound iodine, antistreptolysin-O titer, and latex fixation reaction were normal. Throat culture revealed no beta hemolytic streptococci.

X-ray examination of the chest showed a rounded left ventricular border suggestive of left ventricular hypertrophy. No other enlargement of chambers was evident, and the aortic arch was normal. The lung fields were clear. On lateral tomograms, an irregular calcific density was seen in the region of the aortic valve or ascending aorta.

Electrocardiograms showed normal sinus rhythm at rates of 102 to 120 and normal P-R and QRS intervals. Marked depression of the S-T segment occurred in Leads II, III, and V, and elevation of the S-T segment in Lead V. T abnormalities and prominent Q waves suggested anterior septal myocardial infarction. No digitalis preparation had been



Fig. 1 Photograph of the opened aortic valve. Note thickened cusps, lack of fusion at the commissures, and narrowed ostium of one coronary artery (arrow).

given for at least 4 days before this tracing was recorded.

Hospital course. The patient was febrile during her 6 days in the hospital, with temperatures ranging between 38 and 40°C. Numerous blood cultures failed to reveal any microorganisms and the low-grade bacteremia did not seem to be an adequate explanation for the fever. Even after 2.4 Gm. of salicylate the temperature failed to return to normal. Digitoxin, 0.1 mg. daily, was reinstituted on the fourth hospital day. In the afternoon of the sixth day she suddenly developed tachycardia and irregular respiration and then became unresponsive with no perceptible peripheral pulse or blood pressure. In spite of emergency measures begun within seconds of the cardiac arrest, the patient died.

Autopsy findings

The patient weighed 61 kilograms and was 173 cm. tall.

The heart weighed 400 grams. The left ventricle was 12 mm. thick at the base and the right was 3 mm. The left ventricular chamber was moderately dilated. The aortic ring was 5 cm. in circumference, the pulmonic 6.5 cm. The cusps of the aortic valves were relatively inelastic, thick, and slightly contracted, but were not fused at the commissures (Fig. 1). The anterior leaflet of the mitral valve was markedly thickened by yellow atheromatous plaques. The ostia of the coronary arteries were narrowed to one third of the normal diameter by circumferential, fibrous, pale yellow plaques (Fig. 1). Similar plaques thickened the root of the aorta in the sinuses of Valsalva; there were also patches of calcification in the region of the aortic ring. The coronary arteries had a normal anatomic distribution, but the lumens of the proximal 3 cm. of both the coronary arteries and their branches were narrowed by focal, noncalcified atheromatous plaques. The lumens of the right coronary artery and of the anterior descending branch of the left were narrowed to less than 1 mm. in diameter 3 cm. distal to their origins. The distal branches of all of the major coronary arteries contained a few stenotic areas. The myocardium of the interventricular septum, lateral wall of the left ventricle, and both left papillary muscles contained numerous gray-white scars up to 5 mm. in diameter. The chordae tendineae appeared to be normal. The endocardium and pericardium were normal. MacCallum's patch was not present.

Blocks for microscopic study were taken from the right and left atrial appendages, atria, ventricles and papillary muscles, pericardium, coronary arteries and ostia, and each of the valves. There was evidence of recent myocardial necrosis in sections from the anterior half of the interventricular septum and from the anterior portion of the lateral wall of the left ventricle. Sections from other portions of the left ventricle and the interventricular septum contained focal areas in which myocardial fibers were replaced by scar tissue and hypertrophied myofibers. Aschoff bodies were not found in any sections from the heart. The intramyocardial muscular arteries showed no hyaline thickening and the perivascular connective tissue was normal. Microscopic sections through the aortic valve showed marked thickening of the intima of the aorta in the sinus of Valsalva by nodules of fibrous tissue but contained a few macrophages with vacuolated cytoplasm. Similar fibrous nodules were also present in the sinus pocket. The fibrosa of the cusps was evenly thickened by fibrous tissue but the spongiosa was relatively normal (Fig. 2). The ventricular surface of the aortic cusps was slightly thickened by collagenous fibrous tissue, especially in the area of the subvalvular annulus. The root of the aorta had areas of calcific deposition which extended to the aortic ring. The

Autopsy was performed by Dr. R. H. Lev.



Fig. 2. Ph m rogr ph f s in through aort h w its pocket showing marked thickening of the intim f he aort (I) nd of he fibrosa f the usp (F) nd the relatively uln olved spongiosa (S) and ve I u l Herts s l and eos ×20

of both leaflet of he m l h w h kend by collagen his w more marked in he terior leaflet. The trial surf nd fibrosa were distorted by dense mass of ollage that contained macrophages empty holesterol left and fo l depos of calcified matrix.

All sections of the oronary rteries showed arable degrees of therosclero hange haracterized by proliferated intima large mbers of macrophages with foam plasm fusiform holesterol clefts, nd degener ion of the in ima media, and adventitia. The lumen were ma kedly tenotic especially that of the erior descend ng branch of the left coronary rtery.

Throughout the aorta he int mal surface was covered with fibrous d l tty plaques. Section showed these plaques to be omposed of rying amou t of fibrous tissue hron inflammatory cells, cholesterol left and m cr ophages with foamy cytoplasm. Local area of cal fied letritus were lso present. Only few such plaques were present in the main pulmonary artery.

The skin of the first second nd fourth interphalangeal webs of both hand contained raised lobul ted y llow form plaques l rge 0.5 by 0.2 by 0.5 Sim l lesions 1 cm in diameter were present on both lbows. There w pink, well-defined, subcut neous nodule on the dorsum of the left foot. Microscopic sections of the nodules on the lbow conta ned clusters of macrophages with foamy cytoplasm in the dermis, occasional multinucleated gia t cells w th fusiform left nd few infl mmatory cells. The nodule from the dorsum of the foot wa composed of fibrobl st admixed with collagen fibers f siform left w re l terspersed among the cellular lement but there were no foamy macrophages and only few mononucle cells.

On gross examination the corneas of the eyes appeared t be normal, but microscopically lipid vacuoles and left were seen in Descemet s and Bowman layers.

The g ll bl lder cont ned 1 t 12 of dark green bile nd se kuli l t the mucosal surface wa tudded w th pale y llow flecks. Microscopic lly macrophages w th foamy ytopl sm were present in the l mina propria.

The lungs weighed 1,420 grams and were dark

red. Copious amounts of frothy serosanguineous fluid were present in all portions of the tracheobronchial tree. Microscopically septal capillaries were engorged and most alveoli contained eosinophilic homogeneous material and few hemosiderin-laden histiocytes. Occasional focal hemorrhages in involved groups of alveoli.

The spleen weighed 250 grams. The capsule was tense and the pulp dark red. Microscopically sinusoids were congested, and microscopic hemorrhages were present. The bone marrow from the vertebral bodies was hypercellular but no macrophages with foamy cytoplasm were seen.

The remainder of the gastrointestinal tract, including the liver as well as the genitourinary organs, endocrine glands, brain, dura, leptomeninges, and serous cavities were normal.

Comment

The clinical course and the laboratory and pathologic findings show that this 17 year-old girl who died from the cardiovascular complications of xanthomatosis had acquired aortic stenosis without any evidence of rheumatic heart disease. This case may thus be added to the few previously recorded in which rheumatic fever was not an etiological factor in aortic stenosis.[2]

In the past there has not been complete agreement on the etiology of acquired calcific aortic stenosis. Although as long ago as 1904 Mönckeberg[4] had pointed out differences between the pathologic changes of aortic stenosis caused by rheumatic fever and of that caused by atherosclerosis other workers have considered rheumatic fever to be almost the sole cause of this valvular deformity. Because in the case of familial hypercholesterolemic xanthomatosis the cardiovascular lesions of atherosclerosis often occur in young people, it is easier than in older patients to determine whether aortic stenosis is due to the atherosclerotic changes alone or is superimposed on an earlier rheumatic valve abnormality.

Barr Rothbard and Eder[1] have reported a case of calcific aortic stenosis in hypercholesterolemic xanthomatosis in a 20-year-old man who died from the complications of extensive atherosclerosis. Microscopic examination of the aortic valve revealed lipophages cholesterol clefts and deposits of calcium characteristic of xanthomatosis but neither Aschoff bodies nor other stigmata of rheumatic fever were found in the perivascular connective tissue, myocardium, papillary muscles val e ,

valves, or pericardium. Several other cases of acquired aortic stenosis in patients with hypercholesterolemic xanthomatosis have been reported [3,4] but without specific evidence to establish the presence or absence of antecedent rheumatic fever. In one of these cases the stenosis was successfully corrected by endarterectomy and removal of the obstructing atheromatous plaques.[3]

The available family history of our patient is not extensive but suggests the pattern reported by others, of transmission by an incompletely dominant gene.[11,2] Both parents although not related have elevated levels of plasma cholesterol without symptoms. All 3 of their children had xanthomas 2 of them have died—one, the present case at 17 years of age from coronary artery disease myocardial infarction and aortic stenosis associated with hypercholesterolemia and xanthomatosis the other suddenly at 11 years of age with the cause of death not established by autopsy. The third daughter is living has xanthomas and elevated serum cholesterol but is otherwise asymptomatic.

Rheumatic fever was the clinical impression of the family physician in both sisters who died. However the patient admitted to the New York Hospital had no history of rheumatic fever and there was no bacteriologic or serologic evidence for a preceding group-A streptococcal infection. At autopsy no Aschoff bodies were found in any part of the heart, there was no verrucal endocarditis, and there were no other stigmata of rheumatic fever. In this age group 75 to 95 per cent of the patients who die of rheumatic heart disease have recognizable Aschoff bodies in the myocardium.[11] The absence of rheumatic lesions and the presence of macrophages with foamy cytoplasm and fibrosis typical of atherosclerosis in the aortic valve indicate that the aortic stenosis was due to the hypercholesterolemic xanthomatosis.

In retrospect, it seems to be probable that the younger sister also had only hypercholesterolemic xanthomatosis and not rheumatic feve The diagnosis of rheumatic fever was based on the presence of a systolic murmur and an elevated antistreptolysin-O titer But th murm setting of xanthomatosis may b due to aortic stenos like that of d the elevated antistreptoly-

cates only a previous group-A streptococcal infection

Summary

The case reported is that of a 17 year old girl who died from extensive cardiovascular complications of familial hypercholesterolemic xanthomatosis. Coronary artery disease, myocardial infarction and aortic stenosis were found at autopsy with characteristic abnormalities of xanthomatosis and atherosclerosis The clinical history and laboratory and pathologic findings revealed no evidence that rheumatic fever had caused the aortic stenosis Hypercholesterolemia without xanthomas was found in both parents. All 3 of their children had xanthomatosis and 2 of them died suddenly

REFERENCES

1 Barr D P Rothbard S and Eder H A. Atherosclerosis and aortic stenosis in hypercholesteremic xanthomatosis, J.A.M.A. 156:943 1954
2. Stanley P Chartrand, C and D vignon, A. Acquired aortic stenosis in twelve-year-old girl with xanthomatosis Successful surgical correction, New England J Med. 273 1378, 1965
3 Boas, E P Elster S. K and Adlersberg, D Calcific aortic stenosis Study of serum cholesterol With observations on calcific aortic stenosis in familial xanthomatosis and hypercholesteremia, Am. Heart J 48:485 1954.
4. Friedberg C. K. Diseases of the heart, ed 2, Philadelphia, 1956, W B Saunders Company p. 1041
5 Khachadurian, A. K.: Inheritance of essential familial hypercholesterolemia, Am. J Med. 37:402 1964
6. Mönckeberg, J G. Der normale histologische Bau und die Sklerose der Aortenklappen, Arch path. Anat. 176:472, 1904
7 Karsner H. T and Koletsky S. Calcific disease of the aortic valve, Philadelphia, 1947 J B Lippincott Company
8. Clawson B J Bell E. T and Hartzell T B. Valvular diseases of the heart, with special reference to pathogenesis of old valvular defects, Am J Path. 2 193 1926.
9 Hall, E. M and Ichioka, T Etiology of calcified nodular aortic stenosis, Am. J Path. 16 761 1940.
10. Christian H. A. Aortic stenosis with calcification of the cusps, J.A.M.A. 97 158, 1931
11 Wilkinson C. F J Hand E. A., and Fliegelman, M T Essential familial hypercholesterolemia, Ann. Int. Med. 29:671 1948.
12. Epstein, F H Block, W D Hand, E. A and Francis, T J Familial hypercholesterolemia, xanthomatosis and coronary heart disease, Am. J Med. 26:39 1959
13. Harlan, W R., Jr Graham J B., and Estes, E. H. Familial hypercholesterolemia: A genetic and metabolic study Medicine 45 77 1966.
14. Rothschild, M A., Kugel, M A and Gross, L: Incidence and significance of active infection in cases of rheumatic cardiovalvular disease during the various age period Clinical and pathological study Am Heart J 9:586, 1934
15. Consolo, A. D: Relation of cardiac lesions to the clinical course of rheumatic fever Arch. Int. Med. 69:551 1942.

'Contractility' of the nonfailing hypertrophied heart

Henry S. Badeer, M.D.
Brooklyn, N. Y.

Contractility may be defined as the property of muscle tissue to shorten or to develop tension or both due to the development of intermolecular forces, the exact nature of which is still not clearly defined. Currently, the accepted view for skeletal and heart muscles is the sliding filament hypothesis in which the contractile proteins actin and myosin are involved in the development of such forces. The points of interaction between actin and myosin are referred to as active sites. The contracting muscle as a whole may or may not be allowed to shorten depending upon the existence of external forces (load) that oppose the developing force in the muscle. Thus, the performance of external mechanical work is not essential for muscle contraction. However, for heart muscle in vivo the performance of external work in the form of pumping blood into the arteries is vitally essential for cardiac function.

Contractility of heart muscle may be studied either in the isolated tissue or in the beating heart in situ and the contraction can be either isometric or isotonic, or both. The muscle may be loaded either before (preloaded) or after (afterloaded) contraction has started or both.

Criteria used to assess contractility

One of the important problems is the choice of a suitable criterion (or criteria) to evaluate the magnitude of the contractile process. In isolated muscles, several criteria have been used. The classic approach has been to record contraction isometrically and take the peak force developed as an index of contractility. When the results in different muscles are pooled, the peak force must be related to the mass of tissue and expressed as force per unit mass or, better, as force per unit cross-sectional area of muscle (stress). The role of mass of tissue may be particularly important in the comparison of normal with hypertrophied muscle. Another criterion for contractility is the rate of force development or the time derivative of the force curve (dF/dt). This has been taken to represent a more fundamental aspect of the contractile process in muscle. However, very often the peak contractile force and the maximal rate of force development change pari passu, e.g., increase in initial length, action of catecholamines or Ca^{++}, increase in frequency of stimulation increase both the peak force and the dF/dt. Nevertheless, there is no reason why the two may not be dissociated under other circumstances.

With isotonic contractions it has been reported that the velocity of shortening varies inversely with the load as in skeletal muscle. This is referred to as force-velocity of shortening or simply force-

Received for publication Oct. 3, [illegible].

*Visiting Professor of Physiology, Department of Physiology, State University of New York, Downstate Medical Center, 50 Clarkson Ave., Brooklyn, N. Y. 11203.

velocity relation With large loads shortening is practically nil and the contraction is isometric (P) On the other hand the greatest velocity of shortening occurs when there is no load at all This is difficult if not impossible to obtain experimentally and has been estimated by extrapolating the force-velocity curve to zero load (V_m) According to Sonnenblick V_m should be taken as the criterion for contractility He reported that increasing the initial length of heart muscle does not increase V_m whereas catecholamines increased Ca^{++} or increased frequency of stimulation of isolated muscle do increase V_m Thus if this criterion is accepted an increase in the initial length of heart muscle does not augment contractility despite the fact that the slope of isometric contractile force (dF dt) and the peak tension are increased It is obvious that this viewpoint may be contested

More recent work by Brady[4] and by Sonnenblick indicates that the velocity of shortening of heart muscle for a given load is quite inconstant unlike that of skeletal muscle Hence the choice of a velocity for a given load is somewhat arbitrary This means that the quantitative aspects of the force-velocity curve remain in doubt especially the value of the extrapolated V_m The difficulty has been partly circumvented by plotting the instantaneous velocity force curves at various instants during contraction and the same reciprocal relationship between force and velocity has been noted Sonnenblick[3] reported that increased initial length of heart muscle does not alter the instantaneous force-velocity curve whereas catecholamines distinctly increase the instantaneous velocity for a given force (load) It should be pointed out however that Brady[4] did not always find an inverse relationship between velocity and force or between instantaneous velocity and force Hence the problem remains open to further study

The criteria for the contractility of the pumping heart in situ have been more varied and less clearly defined Some investigators have used cardiac minute output as an index of myocardial contractile force. This is unjustified because an increase in output may be achieved by cardioacceleration only without any change in stroke volume The use of stroke volume is also unjustified since under certain circumstances, stroke volume may decrease or remain constant despite an increase in myocardial force of contraction e.g increasing peripheral resistance with constant venous inflow and constant heart rate A better criterion is the magnitude of the peak pressure developed in a chamber of the heart or still better the maximal rate of rise in pressure (maximal dp/dt)[6,7] Rushmer[8] has recorded aortic flow rate left ventricular pressure and left ventricular diameter in unanesthetized dogs, and with the use of analog computers derived other variables such as stroke volume volume acceleration dp/dt stroke work power etc. He recommends that ventricular contractile function be described in such precisely defined and accepted physical terms. Sarnoff[9] has used the relationship between stroke work and mean atrial pressure as an index of contractility when venous inflow to the heart in situ is acutely augmented by an infusion (ventricular function curve) In the early studies heart rate and aortic pressure were allowed to change in a random fashion during the graded increase in venous inflow Under such conditions increasing stroke work (stroke volume × mean ejection pressure) could be due to an increase chiefly in stroke volume or in aortic pressure or to both to an equal extent. If one remembers that at a given heart rate the capacity of the heart to do volume work is greater than to do pressure work,[10,11] it becomes obvious that the same ventricle can give different function curves depending upon the prevailing arterial pressure and stroke volume Furthermore, Sarnoff[12] has shown that the function curve also varies with heart rate (slower rates giving higher curves) Ideally one should obtain two types of function curves one in which heart rate and aortic pressure are kept constant while stroke volume is increased (volume function curve) and the other in which heart rate and stroke volume are held constant while pressure is increased (pressure function curve) Sarnoff[13] has noted that there is a large family of function curves depending upon the type of load and the existing heart rate Unless these important variables are controlled ventricular function curves

have limited value from a quantitative point of view Goodyer and associates have studied left ventricular pressure curves in closed-chest dogs by progressively obstructing the ascending aorta with a balloon and relating ventricular peak pressure to the ventricular end-diastolic pressure. It was noted that peak ventricular pressure when end-diastolic ventricular pressure was 12.5 mm.Hg ($P_{12.5}$ index) was a useful index of contractile capacity of the left ventricle. This index also closely reflected the maximal peak pressure attained during a short complete obstruction of ventricular outflow Another approach to the study of contractility is the use of strain gauges sutured to the surface of the ventricles to record the force of contraction.[14,18] These methods have their drawbacks and inaccuracies.

More recently contractile tension in the left ventricular wall has been calculated from measurements of pressure and ventricular volumes and the use of the Laplace formula, on the assumption that the cavity is spherical or ellipsoidal If the ventricle is assumed to be a sphere the total force against the wall is equal to the pressure times the internal surface area of the sphere or $P \cdot 4\pi r^2$. This is equal to the sum total of tensile forces in the wall of the entire sphere.[17] The force at the equator separating the two halves of the sphere is $P \cdot \pi r^2$ whereas the force across the wall per unit length of circumference is $\frac{Pr}{2}$. Tension per unit cross-sectional area (stress) of the muscle is $\frac{Pr}{2\delta}$ (δ being the thickness of the wall).[18] There are many practical difficulties in applying these formulas to the pumping heart and the calculation of contractile tension is, at best, a rough approximation.

Finally recent attempts have been made to plot the "force velocity" relationship in the pumping heart.[19-21] Shortening has been measured with callipers on ventricular surface or from determinations of end-diastolic and end-systolic volumes It was found that at any instantaneous muscle length there is a reciprocal relationship between tension or stress and the velocity of shortening similar to that of isolated muscle.[?] Also an increase in end-diastolic volume was found to increase isometric force (P_o) without changing V_{max}.[21]

Before we consider the studies on contractility of the hypertrophied heart, it is necessary to clarify certain definitions or concepts. Contractility may be studied under circumstances that have induced myocardial hypertrophy e.g hypertension valvular stenosis, or regurgitation and be compared with the contractile force of the heart under normal conditions. Here one must distinguish between contractile force of the entire thickness of the wall per unit length of circumference and the force per unit cross-sectional area (stress) across the wall.[22]

Contractility may also be studied by subjecting normal and hypertrophied hearts to progressively increasing loads (increasing inflow or arterial resistance) and determining the contractile capacity or maximal work performance per beat. In all such studies, stroke capacity must be related to the mass of tissue when comparisons are made between hypertrophied hearts and normal controls. It may be useful to remember that the normal heart has a higher capacity for volume work than for pressure work.[9,15]

Myocardial contractility in pathologic conditions associated with cardiac hypertrophy

Sandler and Dodge[22] have calculated the left ventricular contractile force in subjects with valvular disease by using biplane angiocardiography to determine left ventricular dimensions and wall thickness and applying the Laplace formula They noted that in patients with aortic stenosis who showed left ventricular systolic hypertension and hypertrophy the peak contractile force during systole across the entire thickness of the wall was distinctly greater than that of subjects who had normal ventricular pressure On the other hand the force per unit cross-sectional area (stress) of the ventricular wall was of the same order of magnitude in the two groups. This finding suggests that hypertrophy is an adaptive mechanism that increases the mural force of contraction by increasing the thi[...] with a tendency to

tively unchanged There is evidence to believe that this is of functional value from the point of view of expenditure of myocardial energy.[32]

Studies on contractile "capacity" of the hypertrophied myocardium

In isolated strips. In 1961 Kerr and associates[2] induced left ventricular hypertrophy in rats by constricting the ascending aorta with a silver ring. After 21 to 90 days the isolated papillary muscle from the left ventricle was electrically stimulated 12 times per minute. The peak isometric forces developed at different initial tensions were plotted expressing the force per milligram dry weight. It was found that, at all initial tensions, the peak force developed by hypertrophied muscle was significantly greater per unit weight than that developed by papillary muscles from normal rats.

In 1963 Grimm and co-workers[34] restudied the problem using rats after 8 weeks of repeated muscular exercise. In contrast to the findings of Kerr they noted that peak force per milligram wet weight was the same in papillary muscles from hypertrophied left ventricles as that in muscles from normal hearts. They also induced cardiac hypertrophy by constricting the aorta or by constricting the aorta and exercising the animal and again observed no difference between the contractile force of papillary muscles from these animals and that of muscles from normal controls.

Unfortunately the discrepancy between the results of these two groups of investigators has not been resolved.

In the heart-lung preparation. Dieckhoff[36] produced hypertrophy of the left ventricle in cats by injuring an aortic cusp. After a period of 60 to 150 days when hypertrophy was established he corrected the regurgitation with a valve and set up heart lung preparations to determine the maximal volume work and the maximal pressure work per minute that the left ventricle was capable of performing. Four normal and 17 hypertrophied hearts were studied. He found that the hypertrophied heart could do more volume work or pressure work per minute than the normal heart. However he did not relate work "capacity" to the mass of ventricular tissue. In his experiments the mean weights of the left ventricles (including the septum) were 6 63 Gm for normal hearts and 11 2 Gm for hypertrophied hearts. If work is expressed per gram tissue, the normal heart is noted to have a greater minute work "capacity" both in terms of volume and in terms of pressure. Unfortunately heart rates were not given. Hence stroke work capacities which would be more meaningful cannot be calculated.

In the innervated heart in situ. In 1958 Beznak[37] induced left ventricular hypertrophy in rats by constricting the aorta just below the diaphragm with a silver ring. She then infused at increasing rates, a 3.5 per cent solution of polyvinylpyrrolidone and noted the maximal minute output that could be obtained. This was considered to be a measure of the "reserve" force of the heart. In 6 to 10 rats, studied 21 days after aortic constriction the maximal output was 178 ± 11 ml per minute as compared to a maximum of 131 ± 13 ml per minute in normal controls. In both the normal and hypertrophied hearts as the infusion rate was increased there was a progressive fall in arterial pressure and a slowing of the heart rate. Analysis of her graphs indicates that, at maximal output values, the rate of the hypertrophied hearts was slower than that of the normal control hearts, and the mean arterial pressure was higher. This indicates that the maximal stroke work was greater in the hypertrophied heart on account of the greater stroke volume and higher arterial pressure. Unfortunately she did not report data on the left ventricular weights in this group of animals, and one cannot express maximal stroke work per unit mass of tissue. It is difficult therefore, to draw conclusions about the contractile capacity of hypertrophied myocardium from her studies.

Recently Geha and associates[71] induced right ventricular hypertrophy by banding the main pulmonary artery. After 3 to 6 weeks (7 dogs) or 12 weeks (6 dogs) the unanesthetized animals were given an infusion of norepinephrine and the maximal stroke work of the right ventricle was determined. In a control group of 6 dogs the right ventricle was acutely stressed by a partial occlusion of the main pulmonary

artery with a balloon and the animal was given an infusion of norepinephrine. On the basis of the maximal stroke work values in the hypertrophied and normal hearts and ventricular weights, it was concluded that the hypertrophied right ventricle was capable of work levels that were not proportionately less than the increase in muscle mass.

Other investigators have used a different approach namely complete occlusion of the aorta in acute experiments and the recording of the maximal peak left ventricular pressure attained. Krames and Northup[29] in 1964 reported that, in rats in which the hearts were hypertrophied by repeated exercise or hypoxia, the maximal peak pressure developed during complete aortic occlusion was less per gram of tissue than that in normal controls.

Similar results have been obtained by Meerson and associates.[30] They produced stenosis of the aorta in rabbits in order to induce left ventricular hypertrophy. After 4½ to 5 months the chest was opened and left ventricular pressure was recorded by puncture and electromanometer. The ascending aorta was occluded completely for 10 seconds and the maximal ventricular peak pressure was registered (usually the highest value was attained in 3 or 4 seconds). The P_m and tension time index per beat of the maximal beat were used to assess the contractile capacity. Similar data were secured from normal animals. Since left ventricles were of different masses in hypertrophied and normal hearts both P_m and TTI_m were expressed per dry weight of left ventricle. It was found that although the hypertrophied ventricle as a whole could develop a higher P_m and TTI_m than the normal ventricle, these values when expressed per gram dry weight were lower for the hypertrophied ventricle. In other words, the greater maximal pressure that could be developed by the hypertrophied ventricle was not in proportion to the increased mass of tissue.

In the experiments of both Northup and Meerson the end-diastolic volumes of the normal and hypertrophied ventricles during the P_m were unknown. Hence it is not possible to calculate the maximal contractile mural force and stress by using the Laplace formula. Under these circumstances the measurement of pressure may not be a very reliable index of contractile force of the muscle.

From the foregoing presentation it is clear that the dynamics of nonfailing hypertrophied myocardium has not received sufficient attention with the use of newer methods of studying muscle mechanics (calculation of contractile stress rather than the measurement of transmural pressure, study of dp/dt relationships when pressure loads are applied or determination of force-velocity length relationships, etc.) There seems to be much room for fundamental work on this important subject.

Summary

Criteria that have been used to assess contractility of the myocardium both in isolated muscle and in the pumping heart, are reviewed. The distinction between contractility of the heart under a given set of conditions and the contractile capacity under increasing loads is pointed out. In studies comparing the contractility of the normal heart with that of the hypertrophied heart the importance of mass of tissue is emphasized.

Contractile force of the hypertrophied myocardium in pathologic conditions is greater than normal when force is expressed across the entire thickness of the wall per unit length of circumference but appears to be of the same order of magnitude as normal when expressed per unit cross-sectional area (stress).

Studies of contractile capacity of the hypertrophied heart have given somewhat contradictory results. In isolated papillary muscles, Kerr and associates reported greater peak tension from hypertrophied muscle per unit dry weight than from normal muscle whereas Grimm and coworkers reported no difference between normal and hypertrophied muscle per gram of tissue.

In the heart lung preparation Dieckhoff found greater minute work capacity for the hypertrophied left ventricle than for the normal. However if minute work capacity is expressed per gram of tissue, hypertrophied left ventricle is noted to have a lower value. Data were not published on stroke work capacity

In the innervated heart in situ the studies of Beznak suggest a greater stroke work capacity of the hypertrophied left ventricle but her data do not permit expression of stroke work per unit mass of tissue. The studies of Northup and of Meerson indicate that the hypertrophied left ventricle develops greater peak pressure than does the normal ventricle when the aorta is completely occluded but when this pressure is related to the mass of tissue the hypertrophied myocardium develops less pressure than does the non hypertrophied.

In conclusion the contractile capacity of the hypertrophied myocardium seems to be either the same as, or less than that of the normal myocardium per unit mass of tissue. On the other hand the hypertrophied cardiac chamber contracts with a greater mural force than does the normal chamber by virtue of increased thickness or cross-sectional area of the wall. This is of great functional significance as an adaptive phenomenon to a chronic increase in load or to a myocardium weakened by disease.

I wish t tha k Dr. Frederic Ka aler of the Department of Physiology Downstate Medical Center Brookl N Y for critically reviewing the ma uscript

Addendum

After this paper had been submitted for publication Spann Buccino Sonnenblick and Braunwald[22] reported studies on the contractile state of papillary muscles from cat right ventricle made hypertrophic (90 per cent increase in weight) by banding of the pulmonary artery. In animals which showed no signs of heart failure the peak isometric tension per unit of cross-sectional area and the force-velocity curve of papillary muscle from hypertrophied ventricles were significantly lower than those in normal controls.

REFERENCES

1. Abbott B C., and Mommaerts, W F H M A study of inotropic mechanisms i the papillary muscle preparation J Gen. Physiol 42:533 1959
2. Sonnenblick E. H : Force- elocity lations in mammalia heart m scle Am J Physiol 202:931 1962.
3. Sonnenblick F H Implications of muscle mechanics in the heart Fed Proc 21:975 1962
4. Brady A. J Time and displacement dependence of cardiac ontractility: Problems in defining the active state and force-velocity relations, Fed. Proc. 24:1410, 1965
5. Sonnenblick, E. H : Determinants of active tate heart muscle Force elocity instantaneous muscle length time Fed. Proc. 21 (Part I) 1396 1965
6. Reeves, T J Hefner L. L. Jones, W B Coghlan, C., Prieto, G. and Carroll, J The hemodynamic determinant of the r te of change in pressure i the left ventricle during isometric contraction, Am. Heart J 60 745 1960.
7. Siegel, J H and Sonnenblick, E. H : Isometric time-tension elationships as n inde of myocardial contractility Circulation Res. 12:597 1963
8. Franklin, D L Va Citters, R. L., and Rushmer R F Left ventricular f nction described i physical terms, Circulation Res 11 702 1962.
9. Sarnoff S. J Myocardial contractility as described by ventricula function curves Observations on Starling s law of the heart, Physiol. Rev 35 107 1955
10. Evans, C. L nd Matsuoka, Y The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart, J Physiol London 49:378, 1914-1915
11. Gollwitzer Meier K. Die Energetik des Sa getierherzens, Klin. Wchnschr 18:225 1939
12. Sarnoff S. J Bra wald E., Welch G. H., J Case, R B Stainsby W N and Macruz, R Hemodynamic determina ts of oxygen consumption of the heart with special reference to the tension time index, Am. J Physiol. 192 148, 1958
13. Stainsby W N Sarnoff S J Brau wald, E., Case, R B and Welch G H Effect of independent alterations of troke volume, aortic pressure nd heart rat on left entricular f nction Fed. Proc 15 177 1956.
14. Goodyer A. V N Goodkind, M J and Landry A. B Ventricular response t a pressure load Left ventricular function curves in intact animal Circulation Res. 10:885 1962.
15. Cotten, M deV and Bay E. Direct measurement of hanges in cardiac cont actile force Relationship of such measurement t stroke work isometric pressure gradient and other parameters of cardiac function, Am J Physiol. 187 122 1956.
16. Hefner L. L., Sheffield L. T Cobbs, G. C., and Klip W Relation bet een mural force nd press re in the left ventricle of the dog, Circulation Res. 11:654 1962.
17. Rolett, E. L., Yurchak P M Hood W B J and Gorlin, R : Pressure-vol me correlates of left ventricular oxygen consumption i the hypervolemic dog Circulation Res. 18 199 1965
18. Badeer H S. C nt actile tension in the heart Am. Heart J 66 132, 1963
19. I y D I Griggs, D M Jr nd Gree field J C., J My cardial mecha ics: Tension- elocity length lationships of he rt muscle Circulation Res. 14 73 1964
20. Levine H J nd Britman, N A : Force-

velocity relations in the intact dog heart, J Clin. Invest. 43 1383 1964

21 Ross, J J Covell, J W., Sonnenblick, E. H and Braunwald, E. Contractile state of the heart characterized by force-velocity relations in variably afterloaded and isovolumic beats, Circulation Res. 18:149 1966.

22 Sandler H and Dodge, H T Left ventricular tension and stress in man, Circulation Res. 13:91 1963

23 Badeer H. S. Biological significance of cardiac hypertrophy (Editorial) Am. J Cardiol. 14 133 1964

24. Kerr A., Jr Winterberger A. R and Giambattista, M Tension developed by papillary muscles from hypertrophied rat hearts, Circulation Res 9 103 1961

25 German, A. F Kobota, R and Whiteborn, W V Properties of myocardium in cardiomegaly Circulation Res 12 118, 1963.

26. Dieckhoff J Leistungsfähigkeit aortenklappeninsuffizienter Herzen ohne und mit Hypertrophie im Herz Lungen-Präparat, Arch. exper Path. Pharmakol. 182:268, 1936.

27 Beznak, M Cardiac output in rats during the development of cardiac hypertrophy Circulation Res 6:207 1958.

28. Geha, A. S., Duffy J P and Swan, H. J C. Relation of increase in muscle mass to performance of hypertrophied right ventricle in the dog Circulation Res. 19:235 1966.

29 Kramer, B., and Northup, D W Isometric tension development in the hypertrophied heart, Fed. Proc. 23:358, 1964

30. Meerson, F Z., and Pshennikova, M G Effect of myocardial hypertrophy on cardiac contractility Fed. Proc. Translation Suppl. 24 T957 1965

31 Spann, J F J Buccino, R A., Sonnenblick, E. H., and Braunwald, E. Contractile state of the myocardium in ventricular hypertrophy and heart failure, Circulation 34:222, 1966 (Suppl. III)

32. Braunwald, E. Sonnenblick, E. H Spann J F J and Buccino, R. A. Effects of heart failure, ventricular hypertrophy alterations in the thyroid state and denervation on the contractility of isolated cardiac muscle, Abstracts of Conference on Experimental Metabolic Cardiopathies and Their Relationship to Human Heart Diseases, New York Academy of Sciences, New York, Jan. 9-11 1967

Fundamentals of clinical cardiology

Cor pulmonale in children Recognition and management

Anne D. Morgan, M.D.
Gainesville, Fla.

Chronic cor pulmonale has been defined as an increased work load on the right heart resulting from respiratory abnormalities which may be caused by disordered structure and/or function of the airways, parenchyma of the lungs, pulmonary vasculature, or thoracic cage. It does not include diseases primarily affecting the left side of the heart or congenital heart disease which may also produce alterations in the pulmonary circulation and respiratory dysfunction.[1]

Two basic mechanisms are involved in the pathogenesis of cor pulmonale: (1) alveolar hypoventilation, which may be caused by primary parenchymal lung diseases or initiated by conditions outside of the lungs, and (2) anatomic reduction of the pulmonary vascular bed from diseases affecting primarily the pulmonary vessels either by intraluminal obstruction or extraluminal occlusion and/or obliteration. The decrease in the total pulmonary vascular bed initiated by these mechanisms results in increased pulmonary vascular resistance and pulmonary arterial hypertension which impose excessive work on the right ventricle that leads to its eventual hypertrophy and failure.

An understanding of the pathophysiology of the underlying pulmonary disorder initiating cor pulmonale is essential for proper management. Therefore, an etiological classification of cor pulmonale in children has been proposed[1] (Tables I and II) based on which mechanism appears to be of major significance in decreasing the pulmonary vascular bed. This is of more than academic interest because the prognosis of cor pulmonale depends largely on the nature and extent of the etiological condition and its degree of reversibility with optimal therapy.

Diagnosis

The diagnosis of cor pulmonale depends upon several factors. First, there must be a recognized etiological cause such as severe parenchymal lung disease, neuromuscular disease, thoracic deformity, obesity, etc. Secondly, there must be right heart enlargement shown by physical examination, electrovectorcardiography and/or roentgenography. Thirdly, the condition must be distinguished from pulmonary hypertension and congestive heart failure due to congenital or acquired heart disease.

Patients with cor pulmonale due pri

From the Department of Pediatrics, University of Florida College of Medicine, Gainesville, Fla.
Supported in part by Developmental Physiology Training Grant (T1HD-34), Cardiovascular Training Grant (1T 1HE-5493-04) (Ez) (trainee Dr. Morgan) and the Florida Heart Association.
Received for publication Nov. 14, 1966.
Presently Assistant Chief of Pediatrics, National Jewish Hospital at Denver, and Senior Instructor in Pediatrics, University of Colorado Medical Center, Denver, Colo. Address: National Jewish Hospital at Denver, 3800 East Colfax Ave., Denver, Colo. 80206.

Table I. Etiological classification of cor pulmonale in children

Cor pulmonale due to alveolar hypoventilation
- A. Alveolar hypoventilation from primary lung disease
  - 1. Obstructive lung disease
    - a. Cystic fibrosis
    - b. Bronchiolitis
    - c. Bronchial asthma
    - d. Emphysema
    - Chronic obstruction of upper airway
    - f. Bronchiectasis
  - 2. Restrictive lung disease
    - a. Diffuse interstitial fibrosis (Hamman-Rich syndrome)
    - b. Wilson-Mikity syndrome
    - c. Chronic pneumonitis
    - d. Tuberculosis
    - e. Idiopathic pulmonary hemosiderosis
    - f. Bronchiectasis
- B. Alveolar hypoventilation from extrinsic conditions
  - 1. Neuromuscular disease
    - a. Polio
    - b. Guillain-Barré syndrome
    - c. Muscular dystrophy
    - d. Myasthenia gravis
    - e. Amyotrophic lateral sclerosis
  - 2. Thoracic cage deformity
    - a. Kyphoscoliosis
    - b. Pectus excavatum and pectus carinatum
    - c. Spondylitis
    - d. Thoracoplasty
  - 3. Respiratory muscle weakness associated with metabolic or endocrine diseases
  - 4. Respiratory syndrome of obesity (Pickwickian)
  - 5. Congenital anomalies
    - a. Diaphragmatic hernia
  - 6. Respiratory center depression
    - a. Drugs, anesthesia
    - b. Central nervous system disease
  - 7. High altitude

marily to obstructive lung disease characteristically have clinical evidence of hyperinflation including increased anteroposterior diameter of the chest and distant breath sounds and heart sounds. In addition to signs of obstruction of the airways, such as wheezes and rhonchi, respirations are usually slow with a prolonged expiratory phase. There is often dyspnea, orthopnea and a chronic cough. Cyanosis, clubbing and pulmonary hypertrophic osteoarthropathy may be apparent. If there is chronic

Table II. Etiological classification of cor pulmonale in children

Cor pulmonale due to pulmonary vascular disease
- A. Intraluminal obstruction
  - 1. Reactive pulmonary artery vasoconstriction
    - a. Absent pulmonary artery
    - b. Altitude
  - 2. Thromboembolism
    - a. Sickle cell anemia
    - b. Rheumatic fever
    - c. Subacute bacterial endocarditis
    - d. Schistosomiasis
    - e. Ventriculoatriotomy
    - f. Carcinomatosis
  - 3. Primary pulmonary hypertension
- B. Extraluminal occlusion and/or obliteration
  - 1. Alveolocapillary block
    - a. Sarcoidosis
    - b. Collagen diseases
      - (1) Rheumatoid arthritis
      - (2) Disseminated lupus erythematosus
      - (3) Scleroderma
      - (4) Dermatomyositis
    - Pulmonary alveolar proteinosis

retention of CO_2, papilledema may be evident and central nervous system symptoms may be manifested by confusion, somnolence, syncopal attacks, or even coma. In compensated patients downward displacement of the liver from overexpanded lungs may simulate hepatomegaly when the liver may actually be of normal size, but in the presence of decompensation the liver becomes markedly enlarged and tender. There may also be peripheral edema and/or ascites.

In contrast, patients with primarily restrictive lung disease and diffusion impairment (alveolocapillary block) characteristically have tachypnea with rapid shallow respiration and severe dyspnea, especially after exercise. Cyanosis is generally absent or minimal when the patient is at rest but increases markedly after exercise. With cardiac decompensation jugular venous distention with prominent a waves, hepatomegaly and peripheral edema develop. Cardiomegaly is easier to detect clinically in these patients than in those with obstructive lung disease. A left parasternal lift indicates right ventricular hypertrophy and the second heart

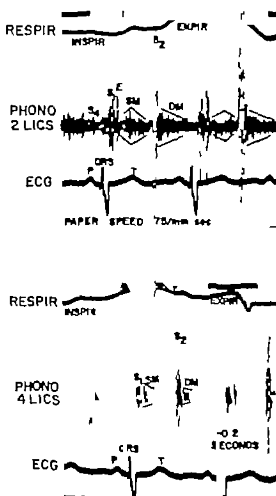


Fig 1 Phonocardiogram of b ld w th severe pulmonary rterial h pertension lemonstrating the pulmonic ejection lick followed by early crescendo-decrescendo tolic ejection murmur Not the accentuat n of the second heart sound nd the decrescendo diastol murmur of pulmonary val insufficiency

sound may be p lpal le over the pulmonic area

Auscultatory findings in patients with cor pulmonale are those characteristic of severe pulmonary artery l hyperten ion A presystolic gallop rhythm may be heard There may be an ejection click and a short systolic ejection murmur maximal in the second left intercostal space from dilatation of the main pulmonary artery The pul monic component of the second heart sound is usually accentuated and i often followed by an early decrescendo diastolic murmur of pulmonic valve insufficiency (Fig 1) A pansystolic murmur along the lower left sternal border maximal in the fourth and fifth intercostal spaces, from dilation of the tricuspid valve annulus caused by tricuspid insufficiency is com mon with failure This murmur is often confused with the murmur of a ventric ular septal defect but the murmur of tricuspid insufficiency usually increases in intensity during inspiration Occasion ally there is a short mid-diastolic, low frequency murmur along the lower left sternal border indicating relative tricuspid stenosis.

Chest roentgenograms frequently aid in determining the underlying type of respiratory disorder Hyperinflation is sug gested by an increased anteroposterior diameter of the chest radiolucency of the lung fields and low flat diaphragms. Obvious thoracic skeletal deformities may be evident. Diffuse interstitial disease may show a characteristic pattern in some cases and cardiomegaly is usually more evident than in patients with obstructive lung disease who often have a relatively small vertical heart roentgenologically even in the presence of cardiac decompensation (Fig 2)

In most patients with cor pulmonale the classic features of pulmonary arterial



Fig 2 Chest roe tgenogr m f 11 old girl ith derm tomyositi nd cor pulmonale N te the diffuse pulmonary infilt tion and bnormally



Fig 3 Posteroanterior and lateral chest roentgenograms of 4 y-year-old child with chronic obstructive lung disease and cor pulmonale from cystic fibrosis. Note the marked increase in the anteroposterior diameter of the chest and flat diaphragms. Pulmonary hypertension is indicated by marked dilatation of the main pulmonary artery and its hilar branches in the posteroanterior projection. Right ventricular hypertrophy is evident on the lateral projection by anterior encroachment of the heart against the sternum.

hypertension with marked prominence of the main pulmonary arteries and diminished peripheral pulmonary vascularity are evident. Right ventricular hypertrophy is best seen in the lateral projection by encroachment of the heart upon the sternum (Fig 3) The left ventricle and left atrium are normal Serial roentgenologic examinations are important in diagnosing the onset of pulmonary hypertension right ventricular hypertrophy and cor pulmonale.

In many patients there is very poor correlation between electrovectorcardiographic findings and the presence of cor pulmonale. However if the onset is in the first decade of life there is more likely to be electrovectorcardiographic evidence of right ventricular hypertrophy than if cor pulmonale does not develop until later The heart may also be displaced from unilateral lung disease or severe thoracic deformity making all electrovectorcardiographic criteria unreliable. Chronic obstructive lung disease often causes a posterior shift of the QRS forces and characteristic electrocardiographic features of right ventricular hypertrophy are modified by abnormalities resulting from anatomic changes in position and rotation of the heart

Right axis deviation is present in most patients with cor pulmonale and there is usually right atrial enlargement manifested by tall peaked P waves greater than 2.5 mm. in amplitude in Leads II III and or aV and diphasic or inverted P waves of increased magnitude in the right precordial leads Right ventricular systolic overload is indicated by tall R waves or qR pattern in the right precordial lead (Fig 4) In patients with severe obstructive lung disease there is often low voltage of the QRS complexes and an rS or QR pattern across the entire precordium (Fig 5)

The electrocardiogram is of greater diagnostic value in patients with primarily pulmonary vascular disease in which the typical pattern of pressure overload of the right ventricle is more likely to be found However in ... study of children with cystic fibrosis, N... and associates found good correlation between pulmonary function tests and electrocardiographic findings of right atrial enlargement right ventricular hypertrophy generalized low

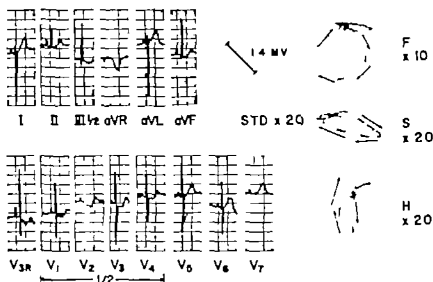


Fig. 4. Electrocardiogr m and ectorcardiogram of a 2 year-old boy with cor pulmonale from chronic obstruction of the pper airw ys (onge ital tracheal web). Note the right axis deviation tall peaked P waves indicating right trial enlargemen t and tall R waves in th right precordial leads indicating right ventricular hypertrophy.

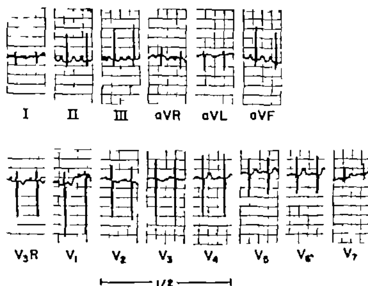


Fig. 5. Electrocardiogram of a 4½-year-old gi l with cystic fibrosis and cor pulmonale. Note the right xis deviation and posterior displacement of the QRS forces indicated by deep S w ves across the entire precordium.

voltage and late R/S progression across the precordium.

Pulmonary function tests will not give an etiological diagnosis of the cause of cor pulmonale but are of value in determining the predominant physiologic disturbance in respiratory function. With obstructive ventilatory insufficiency vital capacity may be close to normal but timed vital capacity expiratory flow rate and maximal voluntary ventilation are markedly re duced and functional residual volume is increased. Reversibility of changes due to bronchospasm can be evaluated by testing

before and after the administration of a bronchodilator drug. Restrictive ventilatory insufficiency produces a decrease in vital capacity and other lung volumes, with relatively less decrease in maximal voluntary ventilation and a normal timed vital capacity.

Measurement of arterial pCO is the most reliable test of the adequacy of alveolar ventilation. The presence of hypercapnia as well as hypoxemia denotes alveolar hypoventilation. With primary pulmonary vascular disease, on the other hand, there is usually compensatory hyperventilation which is effective in eliminating excessive carbon dioxide so that hypercapnia is absent unless an associated restrictive ventilatory defect produces generalized alveolar hypoventilation. In conditions producing an alveolocapillary block, a decrease in diffusing capacity is the earliest abnormality. Arterial hypoxemia may be minimal at rest, but oxygen saturation becomes markedly decreased with exercise.

Pulmonary function tests may be normal in the primary intraluminal pulmonary vascular diseases (thromboembolism and primary pulmonary hypertension). However, in certain cases pulmonary angiography and radioisotope lung scans may be extremely valuable diagnostic tools. Cardiac catheterization, although potentially hazardous, is usually necessary to document the presence of precapillary pulmonary hypertension and eliminate a cardiac defect as the cause.

Treatment

Treatment of cor pulmonale must be aimed at correction of the underlying pulmonary disease, if possible and maintenance of normal gas exchange. Basically, the general principles of therapy include measures to insure adequate alveolar ventilation, good tracheobronchial hygiene, normal acid-base balance, and control of cardiac decompensation.

A. Alveolar ventilation

1. OXYGEN. An adequate level of oxygenation should be maintained at all times. Humidified oxygen at 40 to 60 per cent concentration is usually adequate. In patients with obstructive lung disease associated with hypercapnia, the administration of oxygen is not without danger because elimination of the hypoxic drive to respiration in the face of a respiratory center no longer responsive to CO_2 may precipitate dangerous CO narcosis. However, very low flow rates of only 1 to 2 liters per minute may be of great benefit to these patients by inducing some vasodilatation of the pulmonary vascular bed. In patients with cor pulmonale resulting from primarily pulmonary vascular disease in the absence of hypercapnia, oxygen can be administered without danger.

2. MECHANICAL ASSISTANCE. Mechanical aids to insure adequate minute ventilation may be necessary, especially in some of the neuromuscular disorders. Mechanical assistance must also be available during oxygen therapy for patients with hypercapnia. Intermittent positive pressure breathing (IPPB) is often helpful in chronic obstructive lung disease. It must be used cautiously, however, in patients with severe air trapping, because the rise in intrathoracic pressure during inspiration may impede venous return to the heart. A total body respirator is rarely required in children, but it may be indicated in some neuromuscular diseases.

3. TRACHEOSTOMY. Tracheostomy will increase effective alveolar ventilation by reducing the anatomic dead space 50 per cent. If bronchial secretions are not too thick, a cuffed tracheostomy tube can be used with a cycled respirator attached to the tube. In children in whom the need for an artificial airway is not anticipated to be over 7 days, nasotracheal intubation is preferable for mechanical ventilation and the removal of secretions.

B. Tracheobronchial hygiene

Maintenance of good tracheobronchial hygiene is essential for assuring adequate alveolar ventilation. Measures aimed at reducing bronchospasm, removing excessive secretions, and eradicating infection are of the utmost importance.

1. BRONCHODILATORS. If bronchospasm plays a significant role in airway obstruction, bronchodilator drugs are indicated. Isuprel (1:100 or 1:200) by nebulization is often effective. Oral bronc[illegible] such as ephedrine sulfat[illegible] (3 mg [illegible] per day in divided doses) [illegible] For
[illegible]t but [illegible]

chospasm epinephrine (1:1000 aqueous solution) is the drug of choice. 0.1 to 0.3 ml. should be given subcutaneously and it may be repeated at 20-minute intervals for a total of three doses. If the response to epinephrine is good, a longer acting epinephrine preparation (e.g., Sus-Phrine (1:200) 0.1 to 0.3 ml. subcutaneously every 8 to 12 hours) may be employed. Lack of responsiveness to epinephrine (epinephrine fastness) may be due to hypoxemia and acidemia, bronchial obstruction from thick, tenacious mucous plugs, or pneumothorax.

Aminophylline is another very effective bronchodilator which may be given by rectal suppository (5 to 7 mg. per kilogram every 8 hours). In emergency situations it may be administered intravenously in a continuous drip of 5 per cent glucose in water (3 to 6 mg. per kilogram every 8 hours) or as a single dose (3 mg. per kilogram injected over a 15 minute period and not repeated over every 8 hours). Toxic reactions to this drug, however, are not uncommon in children, and overdosage can result in death.

Corticosteroids may be necessary in emergency situations such as severe status asthmaticus, but their long term use in the management of chronic obstructive lung disease is seldom indicated. The untoward side effects of the prolonged administration of steroids (e.g., growth suppression, Cushing's syndrome, hypertension, peptic ulcer, myopathy, diabetes, and electrolyte imbalance) limit their usefulness mainly to life-threatening situations or those conditions which apparently are refractory to other therapy. In acute situations high doses of steroids (e.g., 100 to 400 mg. of hydrocortisone) are generally employed the first day and the dose is then either tapered as rapidly as possible to maintenance levels or withdrawn completely.

2. EXPECTORANTS. Saturated solution of potassium iodide (SSKI) (1 drop per year of age orally every 6 hours) is a useful expectorant to help liquefy and expel secretions. Glyceryl guaiacolate (Robitussin) is another useful expectorant generally readily accepted by children. Antihistamines are contraindicated because of their drying action. Mucolytic aerosol sprays and mist tents are extremely valuable both prophylactically and for intensive therapy, especially in children with cystic fibrosis, to aid in liquification and removal of the abnormal thick, tenacious mucus. Endotracheal suction and bronchoscopy are sometimes necessary to remove excessive bronchial secretions and clear the airways.

3. HYDRATION. Dehydration from vomiting, inadequate intake, and insensible loss of fluid from the increased work of breathing is a frequent accompaniment of obstructive lung disease in children. Dehydration leads to further inspissation of bronchial secretions and contributes further to mechanical obstruction of the airways. Therefore adequate hydration, with intravenous fluids if necessary, is essential in these patients.

4. CONTROL OF INFECTION. Infections must be promptly diagnosed and treated by appropriate use of antibiotics. In selected patients long term antibiotic therapy is sometimes used, but the development of resistant organisms is a serious problem. Influenza vaccine may be of prophylactic value, especially in debilitated children. Routine immunization *should be carried out*, as in all children, unless there is a known contraindication.

5. GENERAL MEASURES. Postural drainage and respiratory exercises are also extremely important aids in the maintenance of good tracheobronchial hygiene. These can be taught to the child or parents and performed routinely at home. Other general measures of importance include avoidance of irritants such as smoke and dust, and avoidance of undue exposure to cold, infection, etc., inasmuch as possible. *Substitution* therapy with pancreatic enzymes or gamma globulin may be indicated in certain patients. Anemia, such as is present with idiopathic pulmonary hemosiderosis, should be corrected by appropriate iron therapy and blood transfusions. If an allergic etiology can be demonstrated, a desensitization program may be beneficial.

C. Acid-base disturbances

1. RESPIRATORY STIMULANTS. In acute respiratory insufficiency with respiratory acidosis, respiratory stimulants *(Emivan)* have been recommended. However, in chronic obstructive lung disease or alveolar hypoventilation resulting from impaired

bellows action of the thoracic cage the increased production of CO_2 from the increased work of breathing may exceed the rate at which it can be eliminated and respiratory acidosis may be aggravated.[6] Furthermore stimulants of the central nervous system generally produce a period of post-stimulatory depression which will increase alveolar hypoventilation and worsen existing acidosis.

2. BUFFERS Intravenous sodium bicarbonate is generally used for the correction of acidosis. In children with chronic lung disease, respiratory acidemia is frequently *complicated by a superimposed metabolic* acidosis from increased metabolism breakdown of body tissues, and reduced renal function associated with dehydration. Correction of acidemia will help relieve bronchospasm and increase alveolar ventilation.[10] The appropriate dosage of sodium bicarbonate may be estimated from the following formula mEq bicarbonate needed = (negative) base excess × 1/4 body weight in kilograms. However if the arterial pCO_2 is already markedly elevated there are theoretical objections to the use of this agent because of further elevation of bicarbonate despite lowering of pH therefore arterial blood gases should be closely monitored in patients with severe respiratory insufficiency. Likewise, electrolyte balance must be monitored in order to avoid excessive depletion of potassium and chloride and hypernatremia which may aggravate congestive failure when there is already cardiac decompensation.

Tris-buffer (THAM) is another potentially useful drug for the treatment of respiratory acidosis.[11,12] It might appear to be preferable to sodium bicarbonate since the buffer action is not dependent on the excretion of carbon dioxide but in some cases it has been shown to decrease ventilation and aggravate hypoxemia. However recently it has been tried with good results in the treatment of status asthmaticus in children.[13]

Acetazolamide (Diamox) a carbonic anhydrase inhibitor has also been recommended for the treatment of chronic respiratory acidosis in adults. It appears to reduce dyspnea, improve exercise tolerance lower arterial pCO_2 and produce diuresis and a metabolic acidosis. Proper evaluation of its use in children with chronic lung disease has not been made but with close monitoring of electrolyte balance it may prove to be safe and beneficial. The production of a metabolic acidosis will enhance the action of thiazide and mercurial diuretics. However the addition of a metabolic acidosis to a severe respiratory acidosis may overwhelm the body's buffers and other homeostatic mechanisms and even result in the death of the patient.

3. OTHER PHARMACOLOGIC AGENTS Recently tolazoline (Priscoline) has been found to be effective in reversing pulmonary hypertension in patients with cystic fibrosis. It may be administered via an indwelling catheter directly into the pulmonary artery. Its action is probably a direct effect on the pulmonary blood vessels which blocks the vasoconstrictive action of hypoxia and acidemia. Theoretically this should be a potentially useful drug for the treatment of many types of hypoxic pulmonary hypertension such as that resulting from obstructive and restrictive chest diseases, obesity etc. Animal experimental studies have already confirmed the importance of vasoconstriction in chronic hypoxic pulmonary hypertension and the rapidity with which the pulmonary arterial pressure can be decreased when the hypoxic stimulus is removed or blocked.[13]

D. Cardiac decompensation

1. DIGITALIZATION Treatment of right heart failure is basically the same as that for congestive heart failure from any cause. This includes bed rest digitalization sodium restriction and diuretics. The value of digitalization in cor pulmonale has been questioned however it is now generally agreed that digitalis is beneficial.[14] Digitalis toxicity may easily be precipitated though especially in the presence of electrolyte and acid base disturbances usually *accompanying chronic respiratory insufficiency* particularly during the relatively rapid changes in blood pCO_2 and concentrations of H, Na and K accompanying assisted ventilatory therapy. The heart rate is not a good indication of adequacy of digitalization since tachycardia will often persist from hypoxic stimulation.

2. SEDATION Sedation with chloral hydrate (*0.25* to *0.5* Gm orally or rectally) or paraldehyde may be helpful in infant

and children with restlessness and apprehension but narcotic drugs should be avoided in the presence of respiratory insufficiency because of their depressant action on the respiratory center

3 PHLEBOTOMY Phlebotomy is sometimes recommended if there is marked compensatory polycythemia since increased viscosity of the blood will increase pulmonary vascular resistance and predispose to the formation of thrombi This procedure however must be undertaken with *extreme caution since acute circulatory* collapse may be precipitated[4] It is probably desirable to reduce the hematocrit to 50-55 volumes per cent which is best accomplished by the removal of small increments of blood at a time and replacement with an equal volume of physiologic saline dextran or plasma

E Pulmonary vascular disease

Therapy of cor pulmonale resulting from primary pulmonary vascular diseases is generally much less successful than that of cor pulmonale resulting primarily from alveolar hypoventilation because conditions in the former group usually have irreversible anatomic changes whereas some degree of reversibility by correction of the hypoxemia and acidemia is often possible in conditions in the latter group Anticoagulant therapy (and surgery in some cases) is recommended for known causes of thromboembolism Steroids have also been suggested in the treatment of diffuse interstitial fibrosis (Hamman Rich syndrome) and idiopathic pulmonary hemosiderosis, but their value has not been proved There is no known effective therapy at present for primary pulmonary hypertension

Summary and conclusions

The prognosis of cor pulmonale depends primarily on the nature and extent of the underlying etiological condition Knowledge of the pathophysiology of the underlying pulmonary disorder responsible for initiating cor pulmonale is essential for proper management.

In the pathogenesis of cor pulmonale alveolar hypoventilation and pulmonary vascular disease are the two basic mechanisms responsible for reducing the total pulmonary vascular bed The resultant increased pulmonary vascular resistance and pulmonary arterial hypertension impose an excessive work load on the right ventricle and lead to its eventual hypertrophy and failure

An etiological classification of causes of cor pulmonale in children has been proposed based on which physiologic mechanism appears to predominate. This has clinical importance for an understanding of the major pathophysiologic derangements and thus the planning of optimal therapy

General principles of treatment include measures aimed at maintenance of adequate alveolar ventilation good tracheobronchial hygiene normal acid-base balance and control of cardiac decompensation Early diagnosis and vigorous therapy may reverse or retard progression of many of the underlying etiological conditions producing cor pulmonale in children and result in a significantly longer survival.

REFERENCES

1 Committee of the World Health Organization Chronic cor pulmonale: Report of an expert committee Circulation 27:594 1963.
2 Morgan, A. D Cor pulmonale in children Review and etiological classification AM HEART J 73:550, 1967
3. Meek, J Anderson, M W Goldberg, H., and Mattingly T W: Chronic cor pulmonale, Dis. Chest 41:177 1962.
4 Massie E., and Walsh T J: Clinical Vectorcardiography and electrocardiography Chicago, 1960 Year Book Publishers, Inc., pp. 19? 216.
5 Ng M Doershuk, C., Liebman, J and Matthews, L. Electrocardiogram in patients with cystic fibrosis and its relationship to functional status as evaluated by pulmonary function tests, (Abstract) Circulation 28 778, 1963.
6 Cherniack R. M and Nlamark, A. The management of chronic respiratory insufficiency in Safar P editor: Clinical anesthesia, respiratory therapy Vol. 1 Philadelphia, 1965 F A Davis, Company pp. 284-309.
7 Lee, G. de J: The circulatory effects of acute respiratory failure: With special reference to acute cor pulmonale, Postgrad. M J 37:31 1961
8. Kroeker E. J and Baylink D J Diagnosis and management of chronic cor pulmonale Postgrad. Med. 33:48, 1963
9 Segal, M S., and Dulfano, M J Management of cardiopulmonary failure, Dis. Chest. 45:24 1964
10. Mithoefer J C., Rosner R H and Karetzky

M. S. The use of sodium bicarbonate in the treatment of acute bronchial asthma, New England J Med. 272 1200, 1965

11. Manaro, D J Katz, S and Luchsinger P C. The use of a carbon dioxide buffer (tris-hydroxymethylaminomethane) in the treatment of respiratory acidosis, Am. Rev Resp. Dis. 86:353, 1962.
12. Bleich, H. L. and Schwartz, W B. Tris-buffer (THAM). An appraisal of its physiologic effects and clinical usefulness, New England J Med. 274 782, 1966
13. Stramm, J Fine R. N Medina, D A., and Donnell G. N The use of THAM in the treatment of tatus asthmaticus, Pediatrics 38:635 1966.
14. Kelminson, L. Cotton, E. K., and Vogel, J H. K.: Reversibility of hypoxic pulmonary hypertension in cystic fibrosis Pediatrics, 39:24 1967
15. Vogel, J H K., Cameron, D and Jamieson, G Chronic pharmacologic treatment of experimental pulmonary hypertension, Am. Heart J 72:50, 1966.
16. Aviado, D M The pharmacology of the pulmonary circulation, Pharmacol Rev 12 159 1960.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reappraisal of digitalis

Part IX. Digitalis toxicity

*Alan F. Lyon, M.D.**
*Arthur C. DeGraff, M.D.***
New York, N. Y.

The toxic manifestations produced by overdosage of cardiac glycosides are of great practical importance to the physician since, in using digitalis effectively, he will necessarily produce toxicity at times because of the narrow range between the therapeutic and the toxic doses. The appearance of any sign or symptom of digitalis toxicity is an urgent indication for adjustment of digitalis dosage, even when the toxic manifestation may appear to be unimportant, such as in those instances of mental confusion or loss of appetite without other toxic manifestations. Unfortunately, central nervous-system, gastrointestinal, or other side effects are soon followed by serious cardiac toxicity. Recent clinical studies have demonstrated that, contrary to prior clinical impression, the commonly used cardiac glycosides produce the same range and frequency of side effects, and that in any individual patient the pattern of toxicity cannot be predicted either on the basis of the glycoside used or the previous responses of the patient. The usual toxic symptoms can be divided into gastrointestinal, nervous-system, and cardiac. The cardiac manifestations are the most important and the most frequent, particularly with rapid intravenous digitalization and when toxicity occurs with too large a maintenance dose. Gastrointestinal side effects are by far the most common during initial oral digitalization.

Cardiac toxicity. Cardiac toxicity is essentially the only cause of death by digitalis. Although arrhythmia is the usual cardiac effect of digitalis overdosage, the possibility has also been raised that digitalis in toxic doses can worsen congestive heart failure even in the absence of arrhythmia. The experimental basis for this rests upon data of 30 years ago, according to which a reduction in the contractility of the isolated cat papillary muscle was noted when exposed to toxic doses of a cardiac glycoside. Clinical observations supporting this observation are scarce and, upon review, do not conclusively document that the increased congestive heart failure can be due to a toxic effect of digitalis independent of arrhythmia in man. Rather, it seems to be reasonable to assume, on the basis of present evidence, that worsening congestive heart failure without arrhythmia is an indication for more rather than less digitalis.

The arrhythmia and combinations of arrhythmias that can result from digitalis

Received for publication Jan. 27, 1967.
*Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N. Y.
**Professor of Therapeutics, New York University School of Medicine, and Consultant in Cardiology, Veterans Administration Hospital, Bronx, N. Y.

overdosage are many Almost all known arrhythmias can be produced by digitalis but some occur with greater frequency than others. Increased ventricular irritability is very common and is manifested by ventricular premature contractions ventricular tachycardia and ventricular fibrillation Ectopic foci of the re-entry type due to local block and dependent on the sinus beat do occur but the type due to increased automaticity of the Purkinje fibers is most characteristic These are identified by their independence from the sinus beat. When the sinus rate is slowed by carotid sinus pressure an independent dissociated ventricular rhythm is produced Either type can be multifocal and either can develop into a ventricular tachycardia. Regular bidirectional ventricular tachycardia is almost solely due to digitalis.

Another common arrhythmia similar in genesis is an ectopic focus producing a normal QRS complex without retrograde P waves called nonparoxysmal nodal or bundle of His tachycardias. When this focus of increased automaticity is relatively slow but faster than the sinoatrial pacemaker incomplete A-V dissociation results.

In addition atrial and A-V nodal premature beats as well as atrial tachycardia can occur Atrial tachycardia with block is due to digitalis far more frequently than to any other cause. Documentation is difficult, but many clinicians are convinced that it has become much more frequent since the advent of thiazide therapy and the increased frequency of chronic potassium depletion Digitalis-induced atrial tachycardia differs from ordinary atrial tachycardia not only in the presence of some A-V block but also in a wider range of atrial rates (130 to 270 or more) slight but measurable irregularity of the atrial rate, and increasing A-V block on carotid sinus pressure. It should be suspected in any patient in whom the cardiac rate accelerates during digitalization and should be tested for by response to carotid sinus pressure

Atrial fibrillation is a relatively uncommon but not rare manifestation of digitalis intoxication It usually occurs at a slow rate because of associated A-V block, but atrial fibrillation with a rapid ventricular rate can occur Rapid rates in atrial fibrillation are more often seen when the toxicity occurs in a patient who previously had sinus rhythm but acceleration of the ventricular rate in pre-existing atrial fibrillation has also been noted

The occurrence of atrial flutter as a sign of digitalis intoxication is very rare Review of case reports shows a few that could be interpreted as being either atrial tachycardia with block or flutter on the basis of the illustrations but there are still several clear-cut instances of digitalis-induced atrial flutter Atrial flutter with a rapid ventricular rate is usually evidence of underdigitalization rather than overdigitalization

Depression of the sinoatrial node manifested by sinus bradycardia sinus arrest and sinoatrial block occurs occasionally but depression of A-V nodal conduction is a much more common and important phenomenon P-R prolongation is the most common finding and although not dangerous of itself it is always an indication that digitalis dosage should be reduced Second-degree block is quite common and is almost always of the Wenckebach type Mobitz block manifested by isolated dropped beats almost never occurs as a sign of digitalis overdosage Complete heart block is a very serious toxic manifestation since it is often associated with an unstable ventricular pacemaker

The duration of cardiac toxicity varies with the rate of dissipation of the particular glycoside It may persist up to 2 weeks when digitoxin is used but is of relatively short duration after digoxin In general manifestations of block appear to persist longer than manifestations of [illegible]

Gastrointestinal toxicity Digitalis frequently produces anorexia nausea and vomiting These symptoms can occur with parenteral as well as with oral digitalis and are mediated largely through the central nervous system Local irritation may also be a factor Diarrhea is less common and its mechanism is unknown Gastrointestinal symptoms [illegible] last more than [illegible] day or two after digitalis is discontinued

Nervous [illegible] The nervous-system effects of digitalis [illegible] central and peripheral Many different manifestations has been

described these have been previously reviewed by us. In addition to the classic visual changes it is important to recall that an organic mental syndrome and even stupor can result from central effects and that a transient but striking peripheral neuropathy can result. An unusual peripheral effect is a reversible exaggerated sensitivity of the carotid sinus reflex producing recurrent syncope.

Factors predisposing to toxicity. The most important factor in predisposing to digitalis intoxication is serious heart disease; it is *in these patients that digitalis will be used* most aggressively. Another important factor is old age when digitalis is poorly tolerated. Renal shut down and chronic renal insufficiency favor toxicity because of the delay in excretion of digitalis. In cyanotic heart or lung disease there is a high incidence of digitalis toxicity because of the additive effect of anoxia on cardiac irritability. Electrolyte disturbances, particularly depletion of potassium in the postoperative patient or in the patient on chronic diuretic therapy are important precipitants of toxicity. In the case of myxedema digitalis is more slowly metabolized; therefore such patients are more sensitive to digitalis.

Acute myocarditis but not chronic cardiomyopathy is likely to be associated with toxic arrhythmias at average doses. Chronic congestive heart failure is associated with progressive sensitivity to digitalis. Whether this is due entirely to the progressive depletion of potassium characteristic of chronic heart failure with or without diuretic therapy or to some other cause is not known.

Finally it has been suggested that patients with chronic atrial fibrillation who are receiving reserpine are more likely to develop ventricular premature contractions on digitalis therapy than those not receiving reserpine. This is difficult to understand since the effect of reserpine in depleting cardiac catecholamines would be expected to reduce the incidence of arrhythmias, but it is well documented.

Digitalis allergy. Allergic reactions to digitalis are rare and cannot be considered to be true toxicity since the reactions are not related to dosage.

Various skin reactions such as an erythematous exanthem, urticaria, papular and vesicular rashes, angioneurotic edema have been described occasionally. There is no information about the value of desensitization in these conditions but passive transfer of skin sensitivity has been accomplished.

Hematologic manifestations include thrombocytopenic purpura and isolated eosinophilia. *There is some cross-over of* allergy between different glycosides. Allergic reactions can occur in the central nervous system. A single well-documented case describes a child who developed fever, opisthotonus and focal neurological signs with digitalis; the symptoms recurred after a small test dose.

Another unusual side effect is unilateral or bilateral gynecomastia that can occur with chronic therapy possibly due to the steroid effect of digitalis. Demonstrable estrogenic changes that can be seen in the vaginal mucosa of postmenopausal women on chronic therapy may have a similar basis.

REFERENCES

1. Rosenberg, M. S., and Graettinger, J. S.: Digitalis intoxication—Management and prevention, DM, November 1962, pp. 1-6.
2. Dick, H. L., McCawley, E. L., and Fisher, W. A.: Reserpine-digitalis toxicity. Case reports of cardiac arrhythmias occurring during reserpine-digitalis therapy and review of the literature with supporting animal experiments, Arch. Int. Med. 109:503, 1962.
3. Church, G., Schamroth, L., Schwartz, N. L., and Marriott, H. J.: Deliberate digitalis intoxication. A comparison of the toxic effects of four glycoside preparations, Ann. Int. Med. 57:946, 1962.
4. Friedberg, C. K., and Donoso, E.: Arrhythmias and conduction disturbances due to digitalis, Prog. Cardiovas. Dis. 2:408, 1960.
5. Lyon, A. F., and DeGraff, A. C.: The neurotoxic effects of digitalis, Am. Heart J. 65:839, 1963.
6. Mosko, M. M., and Taylor, R. G.: Digitalis allergy with demonstrable antibody, J. Allergy 25:477, 1954.

Annotations

Emotions and ischemic heart disease

Emotional stimuli affect heart action through the autonomic nervous system and by hormonal influences.

Most of the studies on psychological and emotional factors in coronary heart disease are concerned with emotions caused by stresses, anxieties, and conflicts. The negative and disturbing effect of these emotions on the heart and heart action has been noted. It has been stated that stress affects psyche and, via neurohormonal influences, leads to biochemical changes, such as a decrease in the clotting time and an increase in plasma cholesterol[1-4] and in platelet stickiness.

According to Raab, socioeconomic stresses in civilized society lead to sympathetic overactivity and to an excess production of catecholamines which, in turn, cause oxygen wastage and damage myocardial metabolism. Civilized behavior implies rational restraint from emotionally motivated action, and prevents the acting out of natural drives.

The quoted studies acknowledge the relevance of psychic and neurohormonal influences but emphasize only their noxious role. They relate mostly to the situation of emotion without action, which is typical of civilized behavior.

However, if we consider not so much the general pattern of behavior but the specific civilized pattern of activity, other aspects of psychological influences and neurohormonal processes will appear.

Although the major demands on cardiac performance (and on coronary blood supply) occur during neuromuscular activity, the mechanism of cardiac adaptation to it and its possible impairment has not been considered. Neurohormonal processes play an important part in cardiac functioning and especially in cardiac adaptation to activity. This adaptation leads to an increase in cardiac efficiency with reduction of oxygen consumption per unit of work. Vasomotor adaptation, governed by the autonomic nervous system, is another part of the cardiovascular response to exercise.

Overactive neurohormonal processes, which previous studies have described as noxious, may become necessary when neuromuscular activity is required.

It is suggested that psychological factors (emotional stimuli) may be a booster of neurohormonal processes. Their physiological role in cardiac adaptation to activity should be observed. Lack of this booster under civilized conditions may effect on the mechanism of cardiac adaptation.

Table I

1	Primitive natural pattern
(a)	Emotional stimulus for action ↓
(b)	Autonomic nervous system arousal ↓
(c)	Cardiovascular mobilization ↓
(d)	Efficient adaptation to activity
2	Civilized pattern of behavior
(a)	Emotional stimulus for action ↓
(b)	Autonomic nervous system arousal ↓
(c)	Wasteful cardiovascular mobilization because of rationally suppressed action
3	Civilized pattern of activity
(a)	Rational stimulus for action ↓
(b)	No autonomic nervous system arousal ↓
(c)	Inefficient adaptation to activity with increased demand on coronary blood supply

Table I outlines my main statements on the relationship between stimulus for action and cardiovascular adaptation to activity.

I stress the third part of Table I as a novel approach. To support it I shall review some of the factors of cardiac adaptation to activity and their possible psychological dependence. I shall also review the psychological factors inherent in the civilized pattern of activity of the typical Western man.

It is known that sympathetic tone affects cardiac contraction and, according to Wood,[illegible] increased adrenergic activity is the first cardiac reserve. Gregg[illegible] noted that during excitement, as in cardiac sympathetic nerve stimulation, the heart is able to augment its coronary circulation with an increased coronary flow per beat.

Recent work by Braunwald and associates has shown that during the stress of muscular exercise the function of the adrenergic ner-

stem assumes gre t impo t o These thors fou nd that inhibi on of the adrenerg tem lone prevented the ncrease trok lume wh h normally rs d n ng exercise They oncluded that he t om ners tem play ng f e t l ng the m oc rdium luring exer se t ajor efficienc

Sarnoff nd M t hell tress the role of or epineph ne nd mpa he t m lat m ardiac performance th hanc m rdial ont ac t l t nd the rol ack rises higher relat n o en re la pressure Inc sed m rdial on ac lit lead sho t he ter tole Such shorten ng s d par sou t impor nc ert inal w ther h ardia rt permit longer dia tole w h be ter use la relaxa m d m rdial fibers there is gre er tro la filling nd be ter oronary flow.

Recent udies ha hc d monst ted th t everyda emotional l affec the secret n of techolam nes Emot ons j oked by ict tiou phenomena (movie pla are the mo t f excreted echolamines the le h observed pher bromc t mia

Studies of R shmer[18] es le l that mu lat n of cert ar re of he h poth lam of mpa thet nerves t the he reproduced the pat er of left ent lar re p se t ercise Nervou nfluences of en nal nd en ironmen l nature acid l rd se la response exer ise

These observ ons le l nsider the li k between ps biolog l flue es the aut nom nervou st m nd rd adaptation The li k is of basic biologic l sig f ance

If one onsiders tha neuron sc lar act vit is ps biolog ll determ ned bec use onst t tes ma ascou response t en ironmental in fluences or nner timuli nd hat this ac n ty lis f r mined t ardiov sc lar adapt tion t w ll l obs ous hat ps biologic l etim l ac tivity and dapt tion to t re onsta tly linked

The dj stment mecha sms were est blished t prim tiv evolutionary tage of the history of he h ma species At hat tage action or activ ty ther was reflex or followed stim lus pable of produc ng emotional harges—as, for example in the ase of h nger or sexual desire or he necessity for fight or flight. The stimulus wh h led t activity would provok other physiological reactions des tined to bring he cardiovascular system into maxi mum efficiency during activity.

Thus psy biological influences play part the process of cardiac adaptation t activity

Such influences become more significa t when the stimulus to activity is emotionally harged. Cannon larm reaction with readiness for fight or flight is extreme example. This does not mea that every emotion fa ors cardiac adaptation. One ould expect this pattern t become effecti nd to be integrated with activity when the emotional tim lus for action was related t basic mot tional drives. I these drives there is enhancement of activity with lertnes of the org ism through the reticular facilitatory sy tem high stat of physiological efficiency is achieved. This activa tion control cortical tone muscula activity nd

ymp thetic tone.[18] Cardiovascular adjustment is pa t of this response

Because ad pt tion to acti ity is related t the motiv tion of drive consider tion should be given t the nat re of the moti tions which d tat the ci ilized pattern of activity

If man moti ating forces ha their hierarchy nd range from the most primitiv t the most refined Engel present the following summary of th hierarchy *Hierarchy of motivat g forces related t* ( ) drives rooted in the biology of the orga sm (based on f nd mental biological needs) (l) the prim t y tem to protect gainst bodily damage ( ) affect evolving in the course of de lopment (d) learned signals which provide in formation bout the environment (refers et to ba ic needs nd to dangers) ( ) highly derivati psychic processes related t all of the preceding but operat ng w th less urgency the service of self re lization productiv ty et (They operate ith the gre test degree of tonomy and are the most accessible t control by will)

This hierarchy is one of biological development t means that the primiti drives were established t the same early tage of huma evolution t wh h homeostatic mechanisms were being formed the more recent ha been the ppearance of a drive or of moti tional forc as in (d) nd ( ) the least probable is the existence of ad ptiv mech ism backing the execution of th des

I i ilized societ the ind idual is taught not t select b stimuli to activ ty he range of basic biologic l dri es or in immedi t emotional mpulses. By rtue of precept nd practice of Western ivilization the "well-socialized ma tend t rt on cerebral orders onl ell w thin tegory ( ), the one w th the lowest motivational force

I tress this "unemot nal activ ty as typical of the Western ma It still requires cardio sc lar adaptation but has no boosting effect on it Action w thout emotion may burden the heart more than "emotion without action which has been often nvoked cause of dise se

Recent psychologic l studies ha produced mple evidence that ndividual prone to ischemic heart dise se follow closely the teachings of Western civilization in their behavior nd i their act ity

Osler described the type of person likely t suffer from "angiosclerosi "man who has risen early and lat taken rest who has eaten the bread of caref lness, stri ing for succes is com mercial professional or political life

Du bar Wardwell and associates, Cady and ssociates,[20] Cleveland and Johnson Friedman and Rosenman,[22] and Russek and Zohma describe the coronary patient ma with sustained dri and long-term planner animated by desire for recognition. Highly concerned with socially ac cepted norms nd with ey for the future he exercises great control over his behavior drives, nd impulses his acti ities would be guided rather rationally than emotionally

Our ow tudies[28] have produced further evi dence showing that patient with coronary disease possess a greater measure of rational control tha do the control group. I our tudy it ppeared, as

ell, that t least some of the coronary patients ere temperamentally unsuited to their inhibited behavior

I previous presentation I tried t sum up desirable social qualities of the man of Western societ I also stated that these qualities apparently correspond ith most of the recent findings on candidates for coronary disease

The characteristics of this Typical Western Man are orientation toward the futur by self direction and self-discipline detachment from strong desires for immediat gratification activities oriented tow d potential achievement not for the pleasure of the work itself bouces implemented rationally motivation by responsability not by enthusiasm reliability and dri t ork by rational self-imposition. The foregoing characteristics based on rational control nd related to social lues are part of the precept and practice of civ lized society They are mostl self-imposed or socioeconomicall imposed I emphasize the following facts ( ) the socially desirable qualities of the t pical Western man figure prominently in the psychological make up of the coronary patient (b) the oronary per sonality is at least in part the product of "Western acculturation

The corollary is that some of the increase in coronary heart disease in "Western culture countries may be due to psychological factors inherent in this cultur nd reflected in patterns of behavior nd activity I defined this pa tern as the civilized pattern of human activ t I this pattern, th civilized ma is guided by psychic processes nd motiv tions controlled by ill and reason there is no arousal of emotion nd of the tonomic nervous system cardiac adaptation to activit will lag behind and ill be less efficient The myocardium orks uneconomically is more vulnerable and ages more quickly through ear and tear The coronary system is presented th the demand for extra supply Minor coronary insufficiency may lead t major myocardial damage nd necrosis.

I should like also to emphasize that tresses or tread l situations requiring emergency action or burs of activ ary ately in their emotional implic tions. T some of them as in he case of maternal duties ith many children or on the ba level or in the case of outside aggression her is strong emotional stimulus arousing the autonomic nervous stem and thus gearing the organism int activit These situations are part of hum b tory and ar st ll th us On the other hand the business executi n and medical prac titioner of toda society are often pressed into emergency action hrough conventional signal nd intellec ual labora ion Their mot tion for act on is ra ional nd only remotely related to basic drives their ardiov scular adaptation ill hav no ex ra bo st The emergency activity ill affect he maladapted heart of the doctor more than he ared heart of the mother ttending to her sa teh ill h ld This to me ppears to be the ex plana ion f he controversy about tresses leading to ischemi heart disease man ha been biologically adapted stresses of prim society hich carry ith hem the adequa stimuli for adjustment There is less ad pta ion hen the environmental challenge is perceived and cou tered on the rational level, as often happens in Western society

Conclusions I the exposition of my iew the main point has been that, in Western man emotional preamble to neuromus lar activity is reduced t minimum Stressed also is the point that such emotional preamble has its biological purpose nd is prime mover of cardiov scular homeo-tas is acti ty I think that the purposef lness of hu man emotions is orth emphasizing For some reason (or is t also an influence of ci ilization) most medical thought concentrat usuall on the negativ value of emotions

It may be that in our present society emotions ha lost much of their purposef lness W do not let them be of biological use in our everyda ac ti ties. W do not synchronize ou action th our emotions. But our const t tion nd our ph siological f nctioning are still as they ere 3,000 years go W find, therefore that toda hen activ y is rationall determined nd not emotionally mot ated, the heart is out in t and orks less eco nomically It asks for more from its feeding han nels Ischemic heart disease comes as punishment for living in the age of reason Nemesis for the ma of today hose precept is t act *as homo sapiens* nd not as *Homo sentiens*

S M ac M D
*Department of Cardiology
Royal Perth Hospital
Perth Western Australia*

REFERENCES

1 Weiss, E, Dlin B Rollin H R Fisher H K nd Depler C R Emotional factor in oro nary occlusion, Arch Int Med 99:628 1957
2 Raab, W Civilization-induced neurogenic degenerativ heart disease Cardiologia (Basel 41 10 1962
3 Russek H J and Zohman B C Rel ive significance of heredity diet and occupat onal stress coronary heart disease of oung adult Am J M Sc 235:266 1958
4 Schneider R A Rela ion of stress t clot ng time, relat vi-cosit and cert in other bio phy ical factors of blood in normotensiv and hypertensiv subject Res P Ass Nerv Men Dis 29:818 1950
5 Wertlake, F T Wilcox A A H ley M I and Peterson J F Rel onship of m tal and emotional stres ser m holes er l levels P oc Soc E per Biol & Med 97 163 1958
6. Friedman M R se man R H d Carrol V Changes in he serum hole er l nd bl d lotting ime in men ubjected lic vari tion f occ pa onal stress Cir lation 17 852 1958
7 Shimamoto T The emergency react n in hromboge esis nd herogenesis Am Hea J 66:372, 1963
8. Wardwell, W I Bahnson, C B and Caron, H S Social and ps chologic l factor in coronary heart disease He lth & Human Beh k r l 154 1963
9 Gorlin, R Measurement f coronary flow in

health and disease in Jones, A. M., editor: Modern trends in cardiology, London, 1960, Butterworth.
10. Wood, P.: Diseases of the heart and circulation, London, 1956, Eyre & Spottiswoode, p. 266.
11. Gregg, D. E.: Physiology of the coronary circulation, Abstract of the 35th Scientific Session American Heart Association, Circulation 26:679, 1962.
12. Braunwald, E., Chidsey, C. A., Harrison, C. D., Gaffney, T. E., and Kahler, R. L.: Studies on the function of the adrenergic nerve endings in the heart, Circulation 28:958, 1963.
13. Sarnoff, S. J., and Mitchell, J. N.: The control of the function of the heart, in Handbook of physiology, Section 2, Circulation, Vol. 1, p. 489, Baltimore, 1962, Williams & Wilkins.
14. Levi, L.: A new stress tolerance test with simultaneous study of physiological and psychological variables, Acta Endocrinol. 37:38, 1961.
15. Rushmer, R. F., Smith, O., and Franklin, D.: Mechanisms of cardiac control in exercise, Circulation Res. 7:602, 1959.
16. Dell, P.: Some basic mechanisms of the translation of bodily needs into behaviour, Ciba Foundation Symposium on the Neurological Basis of Behaviour, London, 1958, Churchill, p. 187.
17. Engel, G. L.: Psychological development in health and disease, Philadelphia, 1962, W. B. Saunders Co., p. 27.
18. Osler, W.: Lectures on angina pectoris and allied states, New York, 1897, Appleton, p. 153.
19. Dunbar, F.: Psychosomatic diagnosis, New York, 1943, Hoeber.
20. Cady, L. D., Jr., Gertler, M. M., Gottsch, L. G., and Woodbury, M. A.: The factor structure of variables concerned with coronary artery disease, Behav. Sci. 6:37, 1961.
21. Cleveland, S. E., and Johnson, D. L.: Personality patterns in young males with coronary disease, Psychosom. Med. 24:600, 1962.
22. Friedman, M., and Rosenman, R. H.: Association of specific overt behaviour pattern with blood and cardiovascular findings, J.A.M.A. 169:1286, 1959.
23. Mine, S., Sinclair, G., and Taft, R.: Some psychological factors in coronary heart disease, Psychosom. Med. 25:133, 1963.
24. Mine, S.: The civilized pattern of human activity and coronary heart disease, M. J. Australia 2:87, 1960.
25. Mine, S.: Psychological factors in coronary heart disease, Geriatrics 20:747, 1965.

Disposable guide for introducing catheters into small vessels

The introduction of catheters into vessels of small diameter, especially those found in infants and young children, may be difficult. A metal guide or introducer to aid in inserting catheters, such as the one recommended by Hohn and Vlad, has proved to be valuable, but its disadvantages are that it must be cleaned and resterilized each time that it is used and that different sizes are required for vessels of various sizes. Described here is an inexpensive plastic guide or introducer which can be discarded at the completion of the procedure.

The instrument (Fig. 1) is made of Delrin. The handle is 4.5 cm. in length with a broadened, ridged section at the end for easy finger grip. The guide portion, at a right angle to the handle, is 1 cm. long and tapers from 0.25 cm. in width down almost to a point. The underside is grooved to facilitate introduction of the catheter. The right angled configuration permits the operator to have an unobstructed view of the opening of the vessel.

The guide is introduced into the isolated vessel through a small transverse or longitudinal incision which is made in the usual manner. The tapered end is placed through the incision and is advanced into the vessel a distance varying from 0.2 cm. up to the entire 1.0-cm. length of the introducing portion. As the operator holds the guide in position with one hand, he slips the catheter along its grooved underside into the vessel and then withdraws the guide.

The guide facilitates rapid insertion of the catheter with far less vascular trauma than is produced by the usual method of inserting catheters with the aid of hemostats, forceps, or vein spreaders. This reduction in trauma is important not only when catheters are inserted into veins but especially in more complicated procedures, such as insertion of catheters into arteries. This device has also found

Deposit. The guide was fabricated for us by the Cardiovascular Special Instruments Division of Becton, Dickinson & Company, Rutherford, N. J.

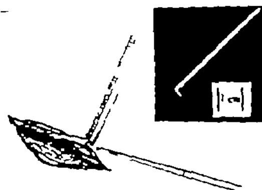


Fig. 1. Use of guide for inserting of catheter into vessel. Inset, Actual photograph of guide.

application when catheters are inserted by cutdown for intravenous infusion. Although planned primarily for children, the tapered design permits the guide to be used in vessels of any size.

Harvey L. Chernoff, M.D.
Marshall B. Kreidberg, M.D.
Department of Pediatrics
Tufts University School of Medicine
and Pediatric Cardiology
New England Medical Center Hospitals
(The Boston Floating Hospital for
Infants and Children)
171 Harrison Avenue
Boston, Mass. 02111

REFERENCE

1. Hohn, A. R., and Vlad, P.: A guide for introducing catheters when cannulating small vessels, Pediatrics 24:636, 1959.

Infusion thrombophlebitis and its prevention

Intravenous infusion is often followed by local thrombophlebitis which can be rather troublesome. Since the generalization of infusion therapy, this problem of infusion thrombophlebitis has gradually received more attention.

Earlier studies to find the predisposing factors have shown that (1) long duration of infusion, (2) acidity of the infusion fluid in long-term infusions, and (3) the use of veins of small caliber increase the incidence of thrombophlebitis. The results have been highly conflicting in regard to other possibly predisposing factors, such as the drugs used, the infusion equipment, the quality of the needles, injection technique, and individual differences between patients (age, sex, etc.). This has obviously been due to the difficulty of standardizing the experimental conditions and, especially, the general tendency to study too many variables in a single, often small material.

Our first study of the problem of infusion thrombophlebitis began in 1963. The conditions of study were as standardized as possible and with sufficiently large material, we concentrated on the following points: (1) the duration of infusion, (2) the role of anesthetic agents, and (3) the role of individual aspects in the genesis of infusion thrombophlebitis. The material of 1,048 infusions was divided into 5 groups. The incidence of infusion thrombophlebitis in the total material was 25 per cent.

The investigation showed clearly the great importance of the duration of infusion, although no infusion lasted more than 8 hours. The incidence of thrombophlebitis in all of the infusion groups subjected to 2-8-hour infusions was over twice that in groups in which the infusions lasted 2 hours. Infusion of 10 per cent invert sugar caused thrombophlebitis more frequently than did injection of 2.5 or 5 per cent thiopental. The administration of barbiturate prior to infusion did not increase the infusion-induced incidence of thrombophlebitis, whereas pethidine increased it by about one third. The incidence of complications was distinctly smaller in patients under 20 years of age than in those of other age groups. Infusion thrombophlebitis was twice as common in women as in men. The incidence of infusion thrombophlebitis in patients with varices of the lower limbs or in patients with a history of thrombophlebitis was no higher than the average.

Ten per cent invert sugar was the basic infusion fluid used throughout the study. The incidence of thrombophlebitis caused by the basic solution itself was 16 per cent for 2-hour infusions, and 40 per cent for 2-8-hour infusions. These complication frequencies were considerably higher than the incidences after infusions of glucose and saline solution of corresponding duration reported earlier in the literature. Since 10 per cent invert sugar is a widely used infusion fluid, we decided to ascertain whether it irritates the veins more than 5 per cent glucose solution. The following test procedure was devised in order to give reliable results. The fluids under comparison were infused at the same rate and for the same length of time into the largest vein in the back of each hand of the patient. Each

solution wa infused turn i t l th hand Th made it impossible t know when exam ning the eins which of the nf sions had been given int which ein W th these l later l nf sions the incidenc f ompl tions as the same fter 10 per cent n ert sugar nd 5 per ent glucose solutions

Although ller result in regard t the sig fic nc f be pH f the f sion fl id h been ont adictory some workers ha f und that ne neut lization f the fusion fluid lower the n idenc of thromt phlet tis Therefore our research team rried out t tudies usi g l l teral inf ions in order t lucidat the role of pH Comparison of the ncidences of thromt phlet sed l y nbuffered nd buffered 10 per ent invert sugar solution sho ed that neutral tion t pH 6 8 lowered the frequenc of ompl tions from 18 t 5 per cent Buffering of th 5 per ent glucose solu t on mi larl lowered th n iden f infusion thrombophlet tis from 20 1 per ent

What then is the linic l rg t nc of infusion thrombophlebitis One third ne fourth of the patients given inf sion her ps suffer from compli tions t gr ter or lesser ex ent Tenderness nd redness of var ing degre be seen near the ei on the first post fusion da few da l ter a gener lly tender palp l le hrombu t the site of injection or in t nediat inity is readily observed by the ph sic d the patient himself Since l f is in thromt phlebit nd the tender thrombus h h arises sequenc of t are f irl ommon nd sometimes trouble the patient for months the prol lem f fusion thromt phlebit s not be dismissed llnic lly Inimg fic t A tention should therefore be paid t proph la m s f as possible

The se of heparinoid ointment has been f ored by some f r proph laxis against fusion thrombophlet The prelim nary result obtained l our ow study rrently in progress suggest that it is poss ble t lower the ncidence of infusion thrombophlet tis slightl nd to m tigate th thrombophlet tis tself th Hirudoid oi tment However effect prophylaxis th Hirudoid ointment routinely is cumbersome procedure Our view based on our ow tudies is that the inconvenience caused to the patients by infusion thrombophlebitis can be eliminated most effecti ely and t the same time most practicably by buffering the infusion fluids W have already tarted with routine buffering of the infusion fl ids nd have not encountered a y detrimental side effects

Hirudoid Luitpold Werk

G staf Elfvi g, M.D
Senior Lect rer Chief Physician
Hyv kää District H pital
Hyvinkää Finland

Ju no Hästbacka M.D
Hel i k F nland

Tapan T mmisto M.D
Hels k Finland

REFERENCES

1 Bolton, Carter J I Reduction in thrombophlel tis by limiting dur tion of intr enou infusions Lancet 2:20, 1951
2 Chvla, G Kli ische nd experimentelle Erfahrungen mit Hirudoid, Deutsche med Wchnschr 79:372, 1954
3 Elf ing G., nd Salkku, K Effect of pH on the incidence of infusion thrombophlebitis, Lancet 1:953 1966
4 Elfving G Silvonen, E., and T mmisto, T i Infusion thrombophlebitl following 10 per cent in ert-sugar nd 5 per cent glucose solutions, Lancet 2:226, 1966 (Letter t the Editor)
5 Gj res, J F Narkotal thrombophlebitis, S enska Läk.tidn. 50 1825 1957
6. H stbacka J T mmisto, T Elfving G., nd Tlit nen, I Infusion thrombophlebitis, Acta Anaesth. Scandina 10:9 1966.
7 Page P H Raine G., and Jones, P F Thrombophlebitis following intravenous infusions, Lancet 2 778 1952
8 Skajaa, T D hl J Jensen, J K nd Kvleselgaard, N Frekvensen f overfladisk t ombeflebitter efter intra enos infusion Nord. Med. 66 1447 1961
9 Vere D W Sykes C H nd Armitage P Venous thrombosis during dextrose nfusion, Lancet 2:627 1960.

Vitamin D as a cause of the supravalvular aortic stenosis syndrome

Before 1958 most textbook on cardiovascular disease either did not mention supraval la aortic stenosis (SAS) or ga the entity only passing mention I that yea Denie nd Verbeuht reviewed the 12 previously reported cases of topsied patients with SAS and described the case of another patient M y of these patients actually had one obstructing band or cord stret hed across the l men of the supra al ula orta and 3 of these patient were probably retarded mentally I 1961

SAS and a parathyroid adenoma were described in a mentally retarded boy who died of nephrocalcinosis and uremia. The same year Wooley and his associates[3] described SAS in several other wise normal members of one family and a familial incidence was subsequently confirmed by others. When the anomaly occurs in familial form, it is thought to be transmitted as an autosomal dominant trait with variable expression. Williams and coworkers, also in 1961 described SAS in a group of retarded patients with mental retardation and peculiar facies. Beuren[4] then extended the features common to the latter type of patient to include stenosis of peripheral pulmonary arteries, dental abnormalities, and strabismus. Subsequently narrowing of peripheral systemic arteries was added to the already impressive list of features of the sporadic form of this disease, which has come to be called the supravalvular aortic stenosis syndrome. Chromosome studies, with one exception, have consistently revealed normal karyotypes. One patient with peculiar facies and mental retardation showed a 46/47 mosaic pattern with an extra chromosome resembling the 19-20 group.

In 1963, Black and Bonham-Carter[6] astutely recognized that the elfin facies observed in patients with severe idiopathic infantile hypercalcemia resembled the peculiar facies observed in patients with the SAS syndrome. Shortly thereafter Garcia and co-workers[8] documented the occurrence of idiopathic hypercalcemia in an infant with SAS, peripheral pulmonary stenosis, mental retardation, and elfin facies in whom the blood level of vitamin D was elevated. The importance of recognizing the association between hypercalcemia and the abnormalities of multiple systems during infancy was later stressed because of the therapeutic implications of early diagnosis and the difficulties encountered in trying to establish a retrospective clinical diagnosis of idiopathic hypercalcemia in the older patient.[16] Recently SAS, mental retardation and peculiar facies was observed in twins[17] and a mentally normal child with congenital hepatic cholesterol-ester storage disease, hypercholesterolemia, and SAS has been studied and operated upon at the National Heart Institute. The latter patient is of particular interest because of the postulated interaction between cholesterol and vitamin D metabolism in the etiology of idiopathic infantile hypercalcemia.

Studies with large doses of vitamin D in nonpregnant animals have emphasized the vascular toxicity of the vitamin. Although the pathogenesis of the abnormalities of the blood vessels remains unclear, it has long been appreciated that excessive vitamin D may produce dose-related vascular lesions ranging from subendothelial edema to calcification.[5-11] A paucity of information exists in regard to the effect on the fetus of induced maternal hypervitaminosis D and until recently there was no direct evidence for transplacental passage of vitamin D.

Because it was not known whether the involvement of multiple systems in the SAS syndrome was genetically determined, or whether some or all of the features were related to deranged maternal or fetal vitamin D metabolism or a combination of genetic and in utero factors, large amounts of vitamin D were administered to pregnant rabbits in a preliminary exploration of the relationship between hypervitaminosis D in the mother and the development of SAS in the offspring.[18] A total of 14 abnormalities of the aorta were noted in 34 offspring whose mothers had received vitamin D. Aortic lesions that resembled those of SAS in man were noted in 8 rabbits. Six additional offspring that were sacrificed at the age of 3 months showed generalized vitamin D vasculotoxicity of an advanced type commonly seen in the adult animal given massive doses of the vitamin but did not exhibit narrowing of the supravalvular aorta. Thirty-three control offspring and 9 rabbits born to mothers on diets deficient in vitamin D showed no abnormalities of the aorta. These results suggested that a derangement of vitamin D metabolism during pregnancy on the part of mother or fetus, or both, may be responsible for SAS, especially when the latter is associated with infantile hypercalcemia. Most recently studies were undertaken to explore the relationship between the characteristic facial and dental features of the SAS syndrome and exposure to vitamin D during pregnancy. Abnormalities of the craniofacial complex have been observed in 70 per cent of the offspring of rabbits given large amounts of the vitamin during pregnancy.[19] The findings resemble anatomically the skeletal and orthodontic manifestations of the SAS syndrome and suggest that the peculiar facies and abnormal dentition, like the aortic lesion, are related to deranged vitamin D metabolism during pregnancy. Because of the poorly understood and highly complex interaction between environmental and genetic factors that are involved in the genesis of human malformations it should be stressed that the studies in rabbits do not provide a simple explanation for the syndrome of SAS and infantile hypercalcemia, but rather raise many questions. It is still not clear why varying sensitivities to vitamin D exist between different individuals of the same species and between different species. Also the differences in sensitivity of various organ systems to the vitamin have not been clarified. Requiring elucidation are the precise role of vitamin D in the etiology of infantile hypercalcemia, the role of prenatal mineral balance and the manner in which excess vitamin D or a lowered threshold to the toxic effects of vitamin D may alter metabolic processes during pregnancy, the time during gestation that vitamin D may interfere with the normal development of the aortic wall, jaws, and teeth and the effects on these lesions of postnatal exposure to vitamin D. In particular the mechanism by which vitamin D produces vascular damage still requires definition. It is not clear whether vitamin D has a local action on vascular tissue or whether it exerts its effects by altering calcium or fat metabolism or in some other undefined manner.

Emphasis on the prophylactic and therapeutic implications of the findings in experimental animals has been deferred until the basic mechanisms involved are clarified further. Spontaneous healing and complete repair of the cardiovascular lesions induced by vitamin D have been reported to occur in experimental animals, a finding which raises the

question of whether prompt diagnosis nd tre t ment of the metabolic disorder in inf ncy may retard the progression of the cardiov scula lesions. Ultimately it is possible that me ns of detecti g pregnancies susceptible t the teratogenic effects of tamin D or related terol may lead to the prevention of the SAS syndrome The mplic tions are sufficient t warra t major effort t obt in epidemiologic genetic metabolic and pathologic information relating to the disease

William F Friedma M D
Cardiolog Branch
National Heart I stitute
Bethesda Md 20014

REFERENCES

1 Denie J J and Verheuht A. I Supravalvular aortic stenosis, Circ lat on 18:902 1958.
2 Perou, M L Congen tal supr al lar aortic stenosis, Arch P th 1 453 1961
3 Wooley C F Hosier D M Booth R. W Molna W Sirak H D and R n, J M Supravalvula aortic stenosis Cli ical experiences with four patient ncluding familial occurrence Am J Med 31 717 1961
4 Kahler R L Br ld F Pla th W H J and Morrow A G F milial occurrence of atrial septal defect with A-V conduction bnormal ties of upr valvula aortic nd pulmonic tenoses, and of ventricular septal defect Am J Med 40:384 1966.
5 Williams, J C P Barratt Boyes, B. G nd Low J B Supr alvular aortic stenosis, Circulation 24 1311 1961
6 Beuren, A. J Apitz, J and Harmjanz, D Supra lvular aortic tenosis in association with mental retardation nd certain facial appearance Circulation 26 1235 1962
7 Beuren, A J Schulze C., Eberle, P Harmjanz, D nd Apitz, J Syndrome of supra val la aortic stenosis, peripheral pulmonary stenosis mental retardation and similar facial appearance Am. J Cardiol 13:471 1964
8. Merritt, A. D Palmer C. G., Lurie P R., and Petry E. I Supravalvular aortic tenosis Genetic nd l ical studies, J Lab. & Clin. Med 62:995 1963
9 Black J A., and Bonham-Carter R. E. Association bet een aortic tenosis nd facies of severe infantile hypercalcemia, Lancet 2 745 1963
10. Garcia, R. E., Friedman, W F Kaback, M M and Rowe R. D Idiopathic hyperc lcemia and supravalvular ortic stenosis: Docume tation of new syndrome New England J Med. 271 117 1964
11 Friedman, W F: Supravalvular aortic stenosis, Am J Dis. Child 109:261 1965
12 Logue H L., J Vogel J H K. Pryor R nd Blount S G Jr Unusual observations in supravalvular aortic tenosis, (Abstract) Circulation 32 II 166 1965
13 Fredrickson, D S.: To be published.
14 Forfar J O Tompsett S. L. and Forshall, W Biochemic l studies in idiopathic hypercalcemia of infancy Arch. Dis. Child. 34:525 1959
15 Duguid J B Vitamin D sclerosis in the rat aorta, J l th. & Bact. 33:697 1930.
16 Ham A. W: Mechanism of calcification in the heart and aorta in hypervitaminosis D Arch. Path. 14:613 1932
17 Gillm n, J and Gilbert, C. Calcium phosphorus nd vitamin D as factors regulating integrity of cardiovascular system, Exper Med. & Surg 14 136 1956.
18. Friedman, W F and Roberts, W C. Vitamin D and the supravalvular aortic stenosis syndrome: The transplacental effects of vitamin D on the aorta of the rabbit, Circulation 34 77 1966.
19 Friedman, W F and Mills, L. S: Production of elfin facies and abnormal dentition by vitamin D during pregnancy: Relationship t the supravalvular aortic stenosis syndrome. Submitted for publication.

Book reviews

Die Herzkatheterisierung bei angeborenen und erworbenen Herzfehlern. By Prof Dr O Bayer, Prof Dr F Loogen and Dr H H Wolter. Stuttgart, 1967 George Thieme Verlag 316 pages. Price DM90

As the title states this volume deals with cardiac catheterization in acquired and congenital abnormalities. This is its second edition.

The authors divide their work into two main sections general and specific. Under the first caption technical equipment is considered. This covers, in cursory fashion such things as instruments for venous cardiac catheterization as well as apparatus for roentgenography angiocardiography and, inter alia technique and apparatus for the various types of gas analysis. The second part deals with methods and ends with a 14-page chapter on complications. Venous catheterization, the authors state carries in adults a mortality of less than 0.1 per cent. They are quick to point out that the risk rapidly increases in children, especially during the first year of life. In a mixed population of their own patients, the author experienced 8 fatalities in 10,000 examinations. The chief causes of death were cardiac arrhythmia (before the availability of electrical defibrillators), the development of severe pulmonary edema in mitral stenosis, and perforation of the heart and coronary venous sinus.

Some 200 pages are allocated to a systematic discussion of cardiac catheterization in congenital abnormalities and in acquired abnormalities. Profuse illustrations help the reader follow the problem that the authors are trying to solve based on their experience with 10,000 cardiac catheterizations.

Professor T Grosse-Brockhoff states in the preface that this volume shows that Germans are capable of the team approach to problems.

The glossy paper and the many illustrations account for the relatively high price of this volume. The cardiologist with a good reading knowledge of German will find this to be a good book to have on his office shelf.

Diagnostik und Therapie der Herzfehler. Vereinigung der Bad Nauheimer Ärzte. Darmstadt 1966 Dr D Steinkopff Verlag 165 pages, 58 illustrations, 23 tables.

The Proceedings of the 31st Western Continuation Course are published in this volume. The thirteen articles cover most fundamental aspects of diagnosis and therapy of the various types of congenital and acquired valvular heart disease and septal defects. Four articles on diagnosis (F Loogen pp. 7-18, M Schlepper pp. 46-65, E. Zdansky pp 66-72 and E Lüthy p. 73-81) include well-established older methods as well as new ones. Lüthy revives the use of the jugular and carotid pulses, which were more frequently used three or four decades ago; their diagnostic value has been recently substantially increased by correlation with catheterization data. Surgery is represented by three articles (F Linder pp 19-23 R. Knebel p 99 and W Knothe, p 122) but the latter's extensive description of blind finger procedures on the mitral valve are outdated by recent advances. Linder presents material of 2,004 operated cases, a valuable addition to existing material. Knebel successfully uses functional exercise tests as indications for heart surgery with changes in the venous pressure (in supine exercise) and the oxygen pulse as principal indices. Physical medicine and rehabilitation including mobilizing the thorax after cardiac surgery is discussed by W R. Ott (pp. 137-150) and dietary and drug treatment by R Aschenbrenner (pp 151-161). The volume contains a short outline of embryological development of the heart as the introductory article (H Rollhäuser pp. 1-6), as well as consideration of pathology (W Sandritter pp 24-30), immunological aspects (K. O Vorlaender and B Sarvan, pp. 31-45) and psychosomatic aspects (L Delius, pp. 82-98). Thus, the volume gives an interesting and informative cross section of present German cardiology.

Hormonii și patologia cardiovasculară. By Iliau Alex Popovici and Victor Săhleanu. Bucharest, 1966 Editura Academiei Republicii Socialiste România

Because this book on the role of the hormones in cardiovascular has been written in Romanian it will be of little use to those who are not acquainted with the language. Although there is a 15-page summary in English it is too brief to be of much value; this is also true of the summary in Russian. Many interesting findings are reported, and there is a review and discussion of the possible influence of the various hormones upon the heart muscle. Electrophysiologic reactions to hormones and diseases of various endocrine glands are included. A fairly good bibliography makes the book a useful source of material on the subject. However those who are interested in detailed data will find it necessary to study the original reports. It is good to have contained in a single volume a summarization of the role of the hormones on the myocardium and its function.

Physical Activity and the Heart. Edited by Martti J. Karvonen, M.D., Ph.D., and Alan J. Barry, Ph.D. Springfield, Ill., 1966, Charles C Thomas. 405 pages. Price $15.50.

This publication of the proceedings of a symposium held in Helsinki, Finland, August 27 to 29, 1964, consists of a series of short papers, all well illustrated and supported by good bibliographies. The proceedings are divided into six parts: (1) testing and cardiovascular dynamics, (2) electrocardiography, exercise, and training, (3) exercise, lipids, and coagulation, (4) coronary heart disease and physical activity, (5) assessment of physical activity, and (6) recommendations for methods and future work. The participants are experts in the field. Among the subjects discussed that are of special interest to cardiologists are electrophysiologic consequences, the electrocardiogram, the vectorcardiogram, standardization of the exercise electrocardiogram, physical activity and coronary heart disease, and cardiovascular studies on endurance athletes.

Physiologists, cardiologists, internists, and students will find this to be a very good book on a much neglected subject.

La Pre-Eccitazione Ventricolare: Contributo Clinico-Sperimentale. By M. Lombardi and G. Masini. Collana di monografie cardiologiche, diretta dal Prof. Luigi Villa, N. 17. Milan, 1966, Recordati Industria Chimica e Farmaceutica s.a.s., 296 pages.

This book is a thorough review of the recent and less recent contributions to the knowledge of the etiology, pathogenesis, clinical features, and electrocardiographic patterns, complications, and therapy of the Wolff-Parkinson-White syndrome. The authors also include a personal study of 43 cases, which have been, in part, examined carefully by pharmacodynamic and functional tests. Some personal opinions of the authors seem to be open to question, particularly those concerning the pathogenesis of the WPW syndrome, which is referred to a peripheral trouble of the atrioventricular transmission at the level of the terminal junctions of the system of His.

The work represents an accurate restatement of the whole subject and is well worth reading.

Die Angiokardiographische Darstellung Kongenitaler Herzfehler: Ein Atlas. By Alois J. Beuren, Helen B. Taussig, and C. Joppich. Berlin, 1966, Walter De Gruyter and Company. 312 pages.

This is an excellent atlas on angiocardiography of congenital heart diseases. The illustrations are good and numerous. The text and legends are good and there is a very comprehensive bibliography. The subject, of course, is not new anymore, but in spite of this students and physicians and especially cardiologists and radiologists will find the atlas to be useful. It is not only a good reference source but also a good book for study by those who may be entering the various fields of cardiology.

The Year Book of Cardiovascular and Renal Diseases (1965-1966 Year Book Series). Edited by Eugene Braunwald, W. Proctor Harvey, John W. Kirklin, Alexander S. Nadas, Oglesby Paul, Victor E. Pollak, Robert W. Wilkins, and Irving S. Wright. Chicago, 1966, Year Book Medical Publishers, Inc. 464 pages. Price $10.

This is another good issue in the yearbook series. Important published papers are summarized for the convenience of the busy physician and for those who wish to review recent publications very quickly. Surely the summaries are no substitute for the original papers, but the reader can obtain the original publications if he desires more detailed information. This publication is highly recommended.

Books received

Differential Diagnosis of Internal Diseases. By J. Julius Bauer. 3rd revised and enlarged edition. New York, 1967, Grune & Stratton, Inc. 1071 pages. Price $29.50.

Modern Treatment. Vol. 4, No. 1, January, 1967. (1) Treatment of Complications of Diabetes, by Charles R. Shuman. (2) Treatment of Pericardial Disease, by Bell M. Cortes. New York, 1967, Hoeber Medical Division, Harper and Row. 1500 pages. Price $16 per year.

Announcement

The Twenty-Fourth Annual Meeting of the American Geriatrics Society will be held on June 16 and 17, 1967, at the Claridge Hotel, Atlantic City, N.J. For further information, write Edward Henderson, M.D., Executive Director, Room 1470, 10 Columbus Circle, New York, N.Y. 10019.

American Heart Journal

June 1967 Volume 73 Number 6

Editorial

The natural history of intracranial aneurysms

George H. du Boulay, M.R.C.P., F.F.R.
London, England

Brolin and Hassler in 1958 drew attention to the frequency of very small presumably early aneurysms easily overlooked at autopsy unless special steps are taken and Hassler[1] has pursued and extended these studies. Stehbens[34] has also found very small dilatations at points where the elastic tissue is degenerate. In his recent paper Sahs[38] illustrates and discusses such microscopic bulges and uses the word "sacculation" which I will adopt to convey the change into frank "berry" aneurysm form. These studies are of the greatest importance in the context of etiology but minute aneurysms cannot be demonstrated by angiography during life; thus from the radiologic and clinical points of view it is the life story of the "saccule" which is at present of greatest moment. From the pathologist's viewpoint Crompton[18] has written very interesting papers about these larger aneurysms.

Statistics and generalizations about frequency, prognosis and treatment[11-47] have been of great value in opening up the subject for investigation but without minute analysis they can obscure the variety of the aneurysms' natural histories and it may be more graphic here to begin by describing a single case. From this by comparisons, some few facts about the life story of the disease may emerge. Perhaps when more data have been accumulated the closest attention to each individual aneurysm may throw light on the prognosis and help in the management of the case.

In 1957 T. B., a 62-year-old woman, suffered two subarachnoid hemorrhages with an interval between them of 3 weeks. Angiography was performed 9 days before her second hemorrhage and as a result of the findings operation upon an anterior communicating aneurysm was carried out 2 days after her second episode of bleeding. At operation, in the angle between the anterior cerebral branches, a bright blue sac was seen; it measured about 4 by 4 mm. (perhaps slightly larger than at angiography) and had a wall that was tissue paper thin. That it was going to burst was obvious as soon as it was touched and in fact during dissection it did burst and came straight off the attachment to the artery. The aneurysm had no neck at all and at its point of departure there was

From the National Hospitals for Nervous Diseases, St. Bartholomew's Hospital and the Nuffield Institute of Comparative Medicine, London, England.
Received for publication Sept. 19, 1966.
Address: Diagnostic Radiology Department, St. Bartholomew's Hospital, London, E.C. England.

just a small opening in the arterial wall. Hemorrhage was controlled by an arterial clip.

The first consideration—perhaps the most important of all—is the actual appearance of the aneurysm at operation. It is clear that the sacculation of this aneurysm was an acute process and that it could not have existed for more than a short time in the state in which it was found. Yet the patient was elderly. Thus a number of central questions about the aneurysmal disease are posed, answers to which would influence the management of the patient even though the actual etiology of the aneurysm remained unknown.

1. What is the time relationship between bleeding and the sacculation of an aneurysm?

2. How prevalent are aneurysms among the general symptomless population?

3. What is the probable future of a symptomless aneurysm found by chance at angiography in a patient with some other condition, or of a symptomless aneurysm in a patient with multiple aneurysms?

In answering the first question about the time relationship between formation of the aneurysm and bleeding, one must know whether the patient already described was typical, for in her case at least there can be little doubt that the macroscopic aneurysm was of very recent origin.

Out of a series of patients at the Maida Vale Hospital, there were 83 in whom the aneurysm responsible for hemorrhage was seen and carefully examined at operation or autopsy. Detailed notes of the operative appearance were made for the most part by Mr. Valentine Logue, and in 33 cases we have from the operation (or occasionally the autopsy) an exact description of the wall of the aneurysm.

In 11 of these 33 cases the whole wall of the aneurysm was tissue paper thin. Most were unilocular. Five of them were surrounded by granulation tissue or adhesions whose firmness and organization seemed to be a good reflection of the interval since hemorrhage. From all of them, hemorrhage had been recent.

In the other 22, however, some part—usually the neck and often also a proximal loculus of the aneurysm—was thicker than the point, blister, or loculus which represented the rupture. Not all of them had bled more than once. Many had bled only recently.

Thus one is faced with a concept which may be useful—that in relation to the first sacculation of an aneurysm, hemorrhage may be *immediate*, within at the most a few weeks, sometimes no doubt days or hours, or it may be *delayed* until months or more later.

The first sacculation of the aneurysm in such delayed cases may be silent, and the eventual hemorrhage when it comes may be the result of fresh weakening of some part of the now thickened original wall of the aneurysm.

In spite of the fact that in two thirds of the cases hemorrhage appears to have been delayed, it does not necessarily follow that no aneurysm is ever safe from the risk of bleeding. In the first place, the vast majority of hemorrhages from a single aneurysm occur within a few weeks of one another, and if the patient survives this phase of acute instability, recurrent hemorrhage from the same aneurysm months or years later is uncommon. Secondly, it may be demonstrated by angiography[21] as well as at autopsy[22,23,24] that macroscopic aneurysms are far more prevalent in the general population than is frank subarachnoid hemorrhage at the age of greatest risk (perhaps even as much as twenty times as prevalent), and with such a low chance of bleeding, the prognosis of a symptomless aneurysm may surely be considered to be a hopeful one. Thus, to the concept of *immediate* and *delayed* hemorrhage, one may add the third larger group of *aneurysms that never bleed at all*. This aspect of the problem should be borne in mind whenever there is a proposal that all aneurysms in so far as possible should be treated by active measures (including surgical intervention whenever the aneurysm is accessible.)

Patient T. B., the case cited, was seen at a moment of time when she had already had more than one hemorrhage. Although, as has been shown, the thin wall of the aneurysm was characteristic of that in one group of patients, from two other points of view her aneurysm was not altogether typical. Firstly, it was relatively free of surrounding adhesions. In spite of

two hemorrhages, and secondly it consisted of a single smooth loculus. To amplify this statement it is necessary to consider what natural courses of events may afflict an aneurysm once it has formed. Leave aside the serious side effects of arterial spasm. A devastating hemorrhage (it is probably only a few milliliters of blood) is liable to cause death by disruption of the brain but very small leaks may be instrumental in giving rise to adhesions around the aneurysm and to fibrous with thickening of its walls and adhesions to the brain a finding that is common enough. A second hemorrhage if again it is a small one, may then result in a localized intracerebral collection of blood the surface of which is defined by gliosis and fibrosis. The center of this small hematoma may clot or remain as a cavity in communication with the vessel of origin. The appearance changes in and obliteration of such extra loculi and accessory cavities have been observed on repeated angiography when the examination became necessary for clinical reasons and some of them have subsequently been confirmed by the operative findings. It is in such cases very difficult to see any difference between true and false sacs. Some perhaps remain small but others develop by degrees layer upon layer of organizing fibrous tissue in their walls and cause symptoms, not by further hemorrhage so often as by pressure and the occupation of space. Very large *aneurysms* formed in this way are relatively rare but comprise a distinct clinical group of space occupying lesion.

Not by any means are all aneurysms which show loculus formation embedded in the brain however and there are probably other mechanisms by which they form.

Be that as it may recent bleeding and loculus formation are undoubtedly very closely connected more than a third of all aneurysms which bleed and are shown by angiography within the first few weeks reveal more than one loculus, whereas, by contrast aneurysms not responsible for recent hemorrhage are hardly ever loculated in the same way. Some aneurysms have more than two loculi and of course some aneurysms bleed two three or more times but the actual relationship between the number of bleeds and the number of loculi shown angiographically is not a particularly close one. This relationship must be affected by the tendency of loculi to clot spontaneously. Did they not do so the number of loculated aneurysms demonstrated would probably have been greater in the Maida Vale series on which these generalizations are based. In that series, some were actually demonstrated to have gone through the cycle of loculus formation (with bleeding) and loculus obliteration.

The sudden appearance or sudden expansion of loculi is by no means uncommon. If a nerve is compressed or hemorrhage takes place, the expansion of loculus is accompanied by symptoms, but cases have also been seen in which angiography has demonstrated the appearance or expansion of a loculus taking place silently. The obliteration of a loculus after operation such as carotid ligation is also a common phenomenon.

So much then for the dynamic appearance and spontaneous clotting of loculi of aneurysms during their period of instability. The quiet thickening of the aneurysm which turns an exceedingly thin walled bulge into a much more stable and rigid structure is not susceptible to radiologic demonstration but it is probable that the thin wall immediately after sacculation begins at once to grow stronger by the laying down of fresh layers of fibrous tissue. Furthermore, some aneurysms are probably thick walled almost from the beginning because the initial damage to the arterial wall is slight and leads only to an oozing of blood and to the growth of surrounding adhesions before any great expansion takes place.

Sahs[1] illustrates two minute aneurysms capped by proliferated connective tissue. It is no doubt because of the thickness of the wall that most aneurysms of long standing are dormant and silent. Delayed hemorrhage when it occurs seems to be the result of a weakening of the wall of the aneurysm at one point the fresh appearance of thin walled sac (this time a loculus of the original aneurysm) and the beginning again of a cycle of events which once more may lead to devastating hemorrhage or to healing.

The question of etiology is here left unt[illegible]

last and the answers are not all established but the problem is becoming clearer Since Eppinger[13] and Turnbull [14] and particularly since Forbus work[1] describing the presence of defects in the medial muscular coat of the arteries of the circle of Willis and critical papers by Schmidt[15] Strauss and associates [16] Glynn Forster and Alpers [18] Carmichael and many others most aneurysms in the head have been ascribed to two causes (1) congenital weakness of the arterial wall and (2) atherosclerosis with hypertension as a possible factor either in their formation or in their rupture

Another theory with several variations that these aneurysms arise at points at which embryologic vessels have not been completely absorbed was favored by Padget [3] Bremer [4] and Bassett but does not seem to be very probable in the light of recent histologic studies.

It is generally agreed that ectasia of cerebral vessels is a manifestation of atherosclerosis but on the other hand the term berry aneurysms still suggests to many people a lesion of congenital origin Nevertheless many berry aneurysms show atherosclerotic changes and Crawford in 1959 on the basis of postmortem studies, has suggested a combination of the congenital and atherosclerotic causes in various proportions in every case Radiologically *one would like to add that there is no* particular magic about the berry shape and all acutely formed aneurysms in the head even traumatic ones, are liable to take on the same general configuration.

The association of atherosclerosis with intracranial aneurysm is certainly very close. All large aneurysms and many small ones show gross atherosclerotic changes. As Crawford points out severe cerebral atheroma is much more common in patients who die of subarachnoid and cerebral hemorrhage than in those who die from noncerebral and noncardiac causes Atherosclerosis is commonly present in the circle of Willis even in very young patients when aneurysms have been demonstrated and even below the age of 20 years but aneurysm at this age is in any case rare.

The distribution of atherosclerosis in the cerebral circulation is very similar to the distribution of aneurysms both in its predilection for a larger vessel and in the tendency for both conditions to occur most severely and most commonly at arterial branchings.

Macroscopic atheroma has been found in cerebral vessels in almost all cases in the series of patients dying with aneurysm at the Maida Vale Hospital and microscopic evidence of atheroma was seen in the remainder but not necessarily in the immediate vicinity of the aneurysm itself

The *incidence of symptomless aneurysm* in patients with transient cerebral ischemia suffering from occlusive vascular disease seems to be higher than that in patients with tumor and suggests a causative association with atheroma

Bull and his associates[1] and Ratinov[26] have pointed out that atheroma may be diagnosed in its severer form by irregularity of the lumen of cerebral arteries. Using this irregularity as a sign one may demonstrate *that the disease is much more common in* patients who present with symptoms due to aneurysm formation than in those who have no such symptoms and whose arteriograms are normal or reveal the presence of a tumor The association of aneurysm with angiographic evidence of atherosclerosis increases steadily with age and there seems to be some slight sex difference (30 per cent males, 38 per cent females) but increasing frequency of atherosclerosis with advancing age in the tumor series is far less obvious than in the aneurysm series. After the age of 35 in the tumor series the frequency of the finding is steady—between one fifth and one sixth of the patients show definite evidence of irregularity of the vessel walls—and in that series the disease is found in the same proportion of men and women

Atheroma was associated with the formation of aneurysms in one of the very *few animals in which a cerebral aneurysm* has been discovered [27]

In spite of this very close association of two diseases, and in spite *of the influence* of established atheroma on the later stages of large chronic aneurysms, changes which would be universally recognized as atheroma are often not found close to the origins of early aneurysms. The patient used as an example at the beginning of this essay *had* no macroscopic atheroma near the aneu

rysm. The very small aneurysms illustrated by Hassler by Stehbens, and by Sahs are associated with alterations in the elastic of the arterial wall but not with the deposition of fat or with other well-recognized atherosclerotic manifestations.

It seems to be probable that work on the relationship of these alterations in the elastic lamellae to atheroma [1,20,21] will throw light not only on the etiology of aneurysm formation but also on the nature of very early or pre-atheromatous arterial disease.

What then is the role of medial muscle defects? There is no doubt, of course that the openings of most large intracranial aneurysms involve those parts of the artery in which the muscle of the media is deficient this has been shown by many people since Forbus in 1930 There are however a variety of reasons for doubting that it is the absence of muscle which constitutes a congenital weakness reponsible for dilatation of the vessel. Both Stehbens and Sahs have shown that very small aneurysms do not bear a constant relationship to the defects. The aneurysms occur at the distal angle of a point of branching whereas the defects are also found at lateral angles, and in some cases the neck of the aneurysm involves part of a defect, but part also of the neighboring muscular wall Moreover the defects are present in the great majority of cerebral vessels and also in other arteries of the body [20] The normal elastica by itself is sufficient to contain a greatly raised blood pressure It is not correct to speak of muscular defects as congenital abnormalities they are anatomic features presumably having a physiologic purpose.

One may speculate about the function of the so-called defect. The muscle coat of an intracranial artery is arranged almost entirely in a circular (probably a helical) fashion without longitudinal fibers. Consider an artery from which a small bulge protrudes at right angles, and let us suppose that the whole junction is sheathed in muscle so that the coat of the main artery and its branch are completely continuous all around the orifice.

The circle in the diagram (Fig 1,*a*) represents the origin of this small bulge. The force which results from contraction

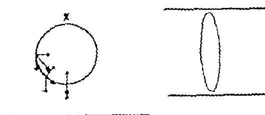


Fig 1 The three small radial arrows represent the force of contraction at the origin of branch entirely sheathed in muscle. The three vertical arrows represent the force of contraction of the parent vessel at those points if that also is sheathed in muscle. The resultants are shown by arrows with double heads. *b* Deformity of the origin of the branch which could result. A fibroelastic pad at X (in) would relieve the origin of the small branch from the effect of contraction of the parent vessel

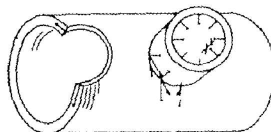


Fig. 2 A three-dimensional representation of the situation. On the left half of the orifice of branch is shown. On the right, the forces are drawn as in Fig. 1,*a*

of its muscle coat may be represented by small radial arrows. The strength and direction of the forces which would be applied at the same points by the contraction of the muscle fibers of the parent artery are also shown in the diagram If the stimulus to contract were applied simultaneously to the muscle coat of both the parent artery and the branch the resultants of these opposing forces would tend to deform the opening of the vessel making it oval shaped (Fig 1,*b*) or even occluding it. The deformity of the origin of the vessel would in any case diminish the cross-sectional area of the branch to a greater degree than if it had remained circular The actual degree of deformity would vary with among other factors, the angle at which the

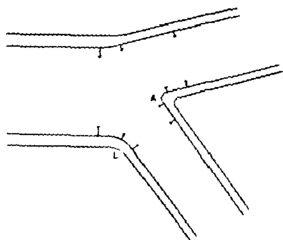


Fig. 3. At Y junctions the muscles of the two branches oppose each other at the distal angle (A) and some elasticity at this point might be expected.

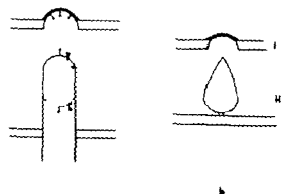


Fig. 4. Very small branches sometimes come off at a tangent from the side of the parent and thus have oval orifices (*a*, *I* section and *a*, *ii* plan). If there were muscle over their outside walls, its contraction might result in the deformity shown in (*b I* section and *b*, *ii*) plan.

branch left its parent. The situation is represented again in three-dimensional form in Fig. 2. The necessity for muscular defects at other points at which they are found is indicated in Figs. 3 and 4.

The provision of a break in the continuity of a muscle near the arterial division—a break filled by a pad of elastic tissue—would clearly go some way to solving these hydrodynamic difficulties, hence perhaps the so-called medial defect.

Intracranial aneurysms seem to be exceedingly rare in animals other than man although the histologic structure of the cerebral arteries is similar in other mammals and all show medial defects at many points of branching.[11,18,20,31]

The mechanical qualities necessary in arterial walls await more profound investigation but it is clear from the survival of some patients with exceedingly thin aneurysms that the mere loss of a layer of muscle from the wall of the artery is likely to be of little consequence. In fact the majority of so-called medial muscular defects in healthy mammalian arteries are well filled with very fine elastic fibers from the adventitia.

Whatever the role of these defects in the formation of aneurysms, it must be a secondary one and they should not be allowed to obscure the main objective when one looks for a preventable or treatable cause. The formation of aneurysms seems histologically to be related to a breakdown of strength and cohesion of the whole of the arterial wall including as well its most important parts—the elastica. It may be that the process which leads to the formation of aneurysms is an acute degenerative incident which in some cases, but not in all, goes on to overt atheroma.

The fact that aneurysms are common *in the head and rare elsewhere need not* imply a primary cause found only in the head but could be explained by different local conditions. The nature of the adventitia of the artery, the concentration of elastic chiefly into the internal elastic *lamina and the striking involvement* of the media in established atheroma may determine the frequency of formation and sacculation of aneurysms.

The possible part played by the adventitia deserves special mention. Within the head the adventitia is exceedingly frail and much of it seems to be ill-suited to be a final defense barrier against the sudden expansion or rupture of an artery whose wall has been damaged by an acute pathologic process. Elsewhere in the body the close investment of arteries by stronger tissues with an independent supply of blood may be thought to be important in preventing the formation of *aneurysms*.

REFERENCES

1. Bassett, R. C.: Intracranial aneurysms, J. Neurosurg. 6:216, 1949.

2. Bremer J. L. Congenital aneurysms of the cerebral arteries. An embryological study Arch. P th. 35:819 1943.
3. Brolin, S. E., and Hassler O.: Minute aneurysms detected by microdissection of basal cerebral arteries, Acta P th. Microbiol. Scandinav 44:59 1958.
4. Bull, J. W. D Couch, R. S. C., Joyce, D Marshall, J Potts, D G., and Shaw D A Observer variation in cerebral angiography An assessment of the value of minor angiographic changes in the radiological diagnosis of cerebrovascular disease, Brit. J Radiol. 33 165 1960.
5. Carmichael, R. Gross defects in the muscular and elastic coats of the larger cerebral arteries, J P th. Bact. 57:345 1945.
6. Carmichael, R. The pathogenesis of noninflammatory cerebral aneurysms, J P th. Bact. 62 1 1950.
7. Chason, J L., and Hindman, W M Berry aneurysms of the circle of Willis Results of planned autopsy study Neurology 8:41 1958.
8. Crawford, T (i) The pathogenesis of therosclerosis The trends of recent work, Proc. Roy Soc. Med. 52:537 1959
9. Crawford, T (ii) Some observations on the pathogenesis and natural history of intracranial aneurysms, J Neurol. Neurosurg & P ychiat. 22:259 1959
10. Crompton, M R The pathology of ruptured middle-cerebral aneurysms, ith special refer ence t the differences bet een the sexes, Lancet 2:421 1962.
11. Crompton, M. R. Intracerebral haematoma complicating ruptured cerebral berry aneury ms, J Neurol Neurosurg & Psychiat. 25:378, 1962.
12. D Bois G. H. Some observations on the natural history of intracranial aneurysms, Brit. J Radiol. 38 721 1965.
13. Eppinger H. Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, Arch klin. Chir Suppl. 35, 1887
14. Forbus W D On the origin of miliary aneurysms of the superficial cerebral arteries B B Johns Hopkins Hosp. 47:237 1930
15. Forster F M and Alpers, B J Anatomical defects and pathological changes in congenital cerebral aneurysms, J Neuropath & Exper Neurol. 4 146, 1945.
16. Friedman, M Pathogenesis of the spontaneous therosclerotic plaque A study on the cholesterol-fed rabbit, Arch. P th. 76:318 1963
17. Gly n, L F Medial defects in the circle of Willis and their relation to aneurysm formation, J P th. Bact. 51:213, 1940.
18. Hassler O (i) Histochemical study of the arterial elastic lamella t the edge of the intracranial berry aneurysms, Acta Soc. Med Upsalien 66:263 1961
19. Hassler O (ii) Morphological studies on the large cerebr l arteries, with reference t the aetiology of subarachnoid haemorrhage Acta Psychiat. Neurol. Scandinav Suppl. 154 1961
20. Hassler O (iii) On the etiology of intracranial aneurysms, *In* Fields, W S and Sahs, A. C., editors I tracranial aneurysms and subarachnoid haemorrhage Springfield, Ill 1965 Charles C Thomas, pp. 25-37
21. Helpern, M and Rabson, S M Sudden and unexpected natural death. III Spontaneous subarachnoid haemorrhage, Am. J M Sc. 220:262, 1950.
22. Housepian, E. M and Pool, J C A systematic analysis of intracranial aneurysms from autopsy file of the Presbyterian Hospital, 1914-1956, J Neuropath. & Exper Neurol. 17:409 1958.
23. Jennings, M A., Florey H. W Stephens, W C., and French, J C Intimal changes in the arteries of pig J Path. Bact. 81:49 1961
24. M Kissock, W Paine, K., and Walsh, E. An analysis of the results of treatment of ruptured intracranial aneurysms, J Neurosurg 1 762, 1960.
25. M Kissock, W Richardson, A. E., and Walsh, E Middle-cerebral aneurysms. Further results in the controlled trial of conservative and surgical treatment of ruptured intracranial aneurysms, Lancet 2 1203, 1960
26. McKissock, W and Walsh, E. Subarachnoid haemorrhage due to intracranial aneurysms. Results of treatment of 249 verified cases, Brit M J 2:559 1956.
27. M Kissock, W Richardson, A Walsh L. and Owen, E M Multiple intracranial aneurysms, Lancet 1:623, 1964.
28. Moon, H. D Coronary arteries in fetuses, infants and juveniles, Circulation 16:263 1957
29. Padget, D H The circle of Willis, Dandy W E editor Intracranial arterial aneurysms, Ithaca, New York, 1944, Comstock Publishing Co. pp. 67-90.
30. Ratinov G. Extradural intracranial portion of carotid artery A clinicopathological study Arch. Neurol 10:66, 1964
31. Sahs, A. L. Observations on the pathology of saccular aneurysms, J Neurosurg 1 793 1966
32. Schmidt, M I tracranial aneurysms, Brain 53:489 1930
33. Stehbens, W E. Intracranial arterial aneurysms, Australasian Ann Med 3:214 1954
34. Stephens W E Medial defect of the cerebral arteries of some mammals Nature 179 327 1957
35. Stehbens, W E Medial defec of the cerebral arteries of man, J Path Bact 78 179 1959
36. Stehbens, W E ( ) Histopathology of cerebral aneurysms, Arch Neurol 8 272 1963
37. Stehbens, W E ( ) Cerebral aneurysms of animals other than man J P th Bact 86 161 1963.
38. Stra ss I Globus, J H nd Ginsburg S W Spontaneous subarachnoid hemorrhage it relation t aneurysms of cerebral blood essels, Arch Neurol & Psy hiat 27 1080 193
39. Turnbull, H M Intracranial aneurysms, Brain 41:50 1918

Clinical communications

The angiographic diagnosis of acute pulmonary embolism: Evaluation of criteria

Paul D. Stein, M.D.
John F. O'Connor, M.D.
*James E. Dalen, M.D.***
*Ali A. Pur-Shahriari, M.D.**
*Frederic G. Hoppin, Jr., M.D.**
David T. Hammond, M.D.
*Florence W. Haynes, Ph.D.**
*Felix G. Fleischner, M.D.***
*Lewis Dexter, M.D.**
Boston, Mass.

Pulmonary angiography is the most specific examination available for the diagnosis of pulmonary embolism.[1-4] Nevertheless, a confident diagnosis of pulmonary embolism on the basis of pulmonary angiography frequently has been impossible because of difficulty in distinguishing abnormalities due to pulmonary embolism from those due to emphysema, bronchiectasis, left ventricular failure, or mitral stenosis.[1-4] This problem of differential diagnosis is especially important because it is in this group of patients, those with lung or heart disease, that the clinical diagnosis by other means is particularly elusive,[5] and it is the debilitated patients, especially those with heart disease, in whom pulmonary embolism most frequently occurs.[5-7]

It is the purpose of this study to assess the specificity of the numerous reported angiographic signs of acute pulmonary embolism in order to determine which angiographic abnormalities reliably indi-

From the Departments of Medicine and Radiology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.

This work was supported in part by Grants from the Life Insurance Medical Research Fund, the National Heart Institute, United States Public Health Service (Grants HE-00430, HTS-5234, and HTS-5590), the American Heart Association, and the Godfrey M. Hyams Trust.

Received for publication July 11, 1966.

*Formerly Assistant in Medicine, Peter Bent Brigham Hospital, and Research Fellow in Medicine, Harvard Medical School. Presently Assistant Director, Cardiopulmonary Laboratory, Baylor University Medical Center, and Assistant Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

**Formerly Associate Staff, Radiology, Peter Bent Brigham Hospital, and Assistant in Radiology, Harvard Medical School. Presently Director of Pediatric Radiology, Boston City Hospital, and Assistant Professor of Radiology, Boston University School of Medicine.

***Assistant in Medicine, Peter Bent Brigham Hospital, and Research Fellow in Medicine, Harvard Medical School.

****Research Associate, Harvard Medical School, and Associate Staff, Medicine, Peter Bent Brigham Hospital.

*****Consulting Radiologist, Peter Bent Brigham Hospital; Emeritus Director of Radiology, Beth Israel Hospital; and Clinical Professor of Radiology, Harvard Medical School.

******Physician, Department of Medicine, Peter Bent Brigham Hospital, and Clinical Professor of Medicine, Harvard Medical School. Address: Peter Bent Brigham Hospital, 721 Huntington Ave., Boston, Mass. 02115.

cate pulmonary embolism irrespective of the presence of coexistent diseases.

Method

Selection of patients. The records of all patients who had selective pulmonary angiograms of technical quality adequate for interpretation were reviewed. There were 71 such patients. A confident retrospective clinical diagnosis of pulmonary embolism or no pulmonary embolism could be made in 52 patients. The findings in these patients constituted the basis of this study.

Clinical diagnosis of pulmonary embolism. A careful evaluation of all available clinical evidence, including radiologic evidence, was made. Stringent criteria were established for the clinical diagnosis of acute pulmonary embolism. Two or three observers reviewed each case in detail. In general, the clinical diagnosis of acute pulmonary embolism was based upon (1) evidence of thrombophlebitis, with the sudden onset of pulmonary or cardiac symptoms, (2) unequivocal evidence of pulmonary infarction, or (3) unequivocal evidence of acute cor pulmonale. The criteria for the clinical diagnosis of pulmonary embolism were kept strict in an effort to avoid false-positive clinical diagnoses. Equal care was exercised to avoid false negative diagnoses. Consequently, the group of patients in whom the diagnosis of pulmonary embolism was uncertain or questionable became relatively large. Of the 71 patients who had adequate pulmonary angiograms, 29 patients clinically had acute pulmonary embolism and 23 patients clinically did not have pulmonary embolism. In 19 patients the clinical diagnosis of pulmonary embolism was uncertain and for this reason these patients were excluded from the study.

Associated clinical conditions. The coexistent cardiac and pulmonary diseases in the 52 patients are listed in Table I.

Angiographic technique. All angiograms were recorded in the anteroposterior projection with the patients lying supine. A U.S.C.I.* No. 7 or 8 catheter with side holes, but no end hole, was positioned in the proximal portion of the main pulmonary artery or the outflow tract of the right ventricle. Angiograms were recorded with the patient in full inspiration during the injection of 40 to 60 ml. of 75 per cent sodium and meglumine diatrizoates (Hypaque M) delivered by a power injector usually at a rate of 30 ml. per second. The first six films were taken at intervals of ½ second. The other six films were recorded at intervals of either 1 or 2 seconds.

Precautions. All patients received an intravenous dose of contrast material 1 or 2 ml. in order to test for immediate sensitivity reactions. Skin tests and a series of graded intravenous injections were performed in any patients who were suspected of allergy and in all asthmatic patients. In all cases, a preliminary injection by hand was made and contrast material was observed fluoroscopically to make sure that the tip of the catheter was free in the ventricle or pulmonary artery.

Complications. Complications of selective pulmonary angiography include the usual complications of right-sided cardiac catheterization.[5] In our group of patients one suffered a perforated right ventricle. This was treated by pericardiocentesis, with good results. The injection of contrast material caused few complications. One asthmatic patient developed bronchospasm and required epinephrine to control whee-

*United States Catheter and Instrument Corporation, Glens Falls, N. Y.

Table I. Associated heart disease or lung disease

Mitral stenosis often associated with other valvular lesions*	13
Emphysema, chronic bronchitis or chronic bronchial asthma†	10
Coronary heart disease or hypertensive cardiovascular disease	9
Rheumatic heart disease exclusive of mitral stenosis	3
Atrial septal defect	2
Constrictive pericarditis	1
No significant heart disease or lung disease	14
Total number of patients	52

*One patient with mitral stenosis also had severe chronic bronchitis.

†Three patients with chronic bronchial asthma or emphysema also had coronary heart disease or hypertensive cardiovascular disease.

ing. Ventricular premature contractions often were noted during injection, but no arrhythmias that required treatment occurred. Some patients suffered nausea and vomiting for a short time after the injection of contrast material.

Angiographic interpretation

All angiograms were studied by two or more members of the group, and all but the most obvious were restudied with the senior radiologist of the team (F. [illegible] F.). The following signs were specifically looked for and noted in each patient: filling defects, cutoffs, pruning, oligemia, asymmetrical filling, prolonged arterial phase, and bilateral lower zone filling delay. Radiologic signs of acute cor pulmonale such as dilatation of the chambers of the right side of the heart, dilatation of the pulmonary artery trunk, and of the hilar arteries were omitted from this study because they can be recognized on the plain roentgenogram.

Filling defect (*Fig. 1*). Any persistent intraluminal radiolucency, either marginal or central, was considered to be a filling defect. This included defects as small as 1 mm in diameter located in distal branches, as well as larger defects in the main branches. Great difficulty was occasionally encountered in the interpretation of smaller changes, and in distinguishing them from summation or subtraction effects due to intersecting vascular or bronchial branches. Some arbitrary decision was unavoidable in borderline situations.

Cutoffs (*Fig. 2*). Any sharp and sudden termination of a branch of the pulmonary artery 0.15 cm or larger was considered to be a cutoff, presumably due to complete occlusion of that branch. Absence of a vessel that was known to have been present by previous angiograms or from anatomic considerations, was considered to be a cutoff even though the point of occlusion was not visualized.

Pruning (*Fig. 3*). If a vessel was clearly visualized and if that vessel showed a paucity of small branches in comparison to comparable vessels in other parts of the lung, pruning of that vessel was said to be present. Although these small branches were presumed to be missing because of occlusion, no sharp termination of these vessels was visualized. This distinguishes pruning from cutoffs.



Fig. 1. Filling defects (*arrows*). Intraluminal radiolucencies, representing the direct shadow picture of the embolic mass, are shown in the left pulmonary artery.



Fig 2 Cutoff (arrows). A sharp termination of some of the third and fourth order branches in the left lower zone is shown. Presumably these cutoffs of branches represent complete occlusion of these vessels.

Oligemia (Fig 4) Areas of increased translucency in comparison with the rest of the lung were considered to indicate diminished perfusion of the area, i.e. oligemia. The increased translucency had to be a constant finding in all of the films of the arterial phase. If the translucent area eventually opacified delayed filling was said to be present in that area rather than oligemia

Asymmetrical filling (Fig 3) If after injection of contrast material into the outflow tract of the right ventricle or proximal portion of the main pulmonary artery sequential films showed one zone filling more slowly than the remainder of the lung then asymmetrical filling was said to be present

In 8 patients included in this study the tip of the catheter was positioned in the very proximal portion of either the left or the right pulmonary artery In those patients symmetry of flow was not assessed

Prolongation of the arterial phase (Fig 3) Lasting filling of a segmental or lobar pulmonary artery when the remainder of the pulmonary arterial branches were properly emptied and the pulmonary veins became opacified indicated prolongation of the arterial phase.

Bilateral lower zone filling delay (Fig 5) If after the injection of contrast material into the outflow tract of the right ventricle or proximal portion of the main pulmonary artery both upper zones filled simultaneously and both lower zones filled more than ½ second later than the upper zones, then bilateral lower zone filling delay was said to be present.

Angiographic criteria of abnormality Angiograms were interpreted as being abnormal if they showed one or more of the following signs filling defects, cutoffs pruning oligemia, asymmetrical filling prolongation of the arterial phase or bilateral lower zone filling delay Angiograms showing none of the above mentioned signs were categorized as being normal

Results

Entire group A confident clinical diagnosis of either acute pulmonary embolism or no pulmonary embolism could be made in the 52 patients studied. The relationship of angiographic abnormality and the clinical diagnosis regarding pulmonary embolism in these 52 patients is shown in Table II Eighty three per cent (24 of 29 patients) who clinically had pulmonary embolism had abnormal angiograms. However 30 per cent (7 of 23 patients) not suspected of pulmonary embolism had abnormal angiograms. The conclusion is that the above-mentioned angiographic signs, although abnormal are not necessarily diagnostic of pulmonary embolism.

The incidence of the specific angiographic abnormalities is categorized in Table III according to the clinical diagnosis of pulmonary embolism. Filling defects cutoffs, and pruning were found only in patients who clinically had pulmonary embolism Oligemia symm[illegible] filling prolongation of the arterial phase



Fig 3 A-C Three films of the same patient taken 1 2 nd 3 seconds respectively after the onset of injection of contrast material t the proximal portion of the main pulmonary artery A One second after injection. There is bsence of opacification the left lower zone indicative of delayed or asymmetrical filling

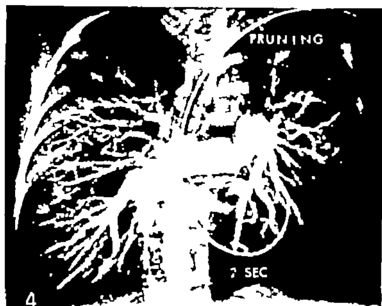


Fig 3 (Cont d). B Two seconds after injection. A paucity of small branches, indicative of pruning is show i the left lower zone This becomes readily pparent when the vessels of the left lower zone are compared t vessels of similar size m similar state of filling in other portions of the lung Such comparison can be made with the vessels of the pper zone shown in Fig 3,A



Fig. 3 (Cont'd). *C.* Three seconds after injection. There is lasting filling of the arteries of the left lower zone whereas the remainder of the pulmonary arteries have emptied and contrast material now opacifies the pulmonary veins. This indicates prolongation of the arterial phase.



Fig. 4. Areas of increased translucency in comparison with the rest of the lung are indicated by arrows. These zones did not opacify on subsequent films, indicating diminished perfusion, i.e., oligemia in these areas.

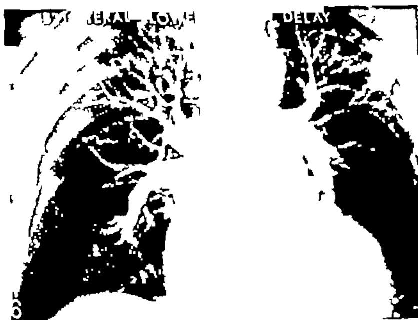


Fig. 5. Bilateral lower zone filling delay. Three seconds after the injection of contrast material into the outflow tract of the right ventricle there is complete filling of the vessels of the upper zone whereas only the main trunks of the vessels of the lower zone have filled. Subsequent films showed a greater than 1½-second delay in the filling of the vessels of the lower zone.

and bilateral lower zone filling delay were found both in patients who clinically had pulmonary embolism and in patients who clinically did not have pulmonary embolism.

Patients without coexistent disease affecting the pulmonary vasculature. Of the 27 patients without the complications of mitral stenosis, lung disease (including asthma), or atrial septal defect (Table IV), 95 per cent (20 of 21 patients) who clinically had pulmonary embolism also had abnormal angiograms, and 83 per cent (5 of 6) who clinically did not have pulmonary embolism had normal angiograms. The incidence of the various angiographic abnormalities found in these 27 patients is listed in Table V. All but one of the patients, who clinically had pulmonary embolism and who had abnormal angiograms, showed filling defects, cutoffs, or pruning. More than one of these signs were usually present. Oligemia was present in 48 per cent (10 of 21) of the clinically positive patients but did not occur in the absence of filling defects, pruning, or cutoffs. Asymmetrical filling, prolongation of the arterial phase, and bilateral lower zone filling delay frequently occurred in combination with the above-mentioned abnormalities.

Patients with coexistent disease that can affect the pulmonary vasculature. Abnormal angiograms were recorded in 2 of 5 patients with tight mitral stenosis and no pulmonary embolism, and in one patient with left ventricular failure* and no pulmonary embolism. Each of these patients showed oligemia as well as asymmetrical filling or bilateral lower zone filling delay. There were abnormal angiograms in 4 of 8 patients with chronic bronchial asthma who were not suspected of having had pulmonary embolism. Three of these patients showed oligemia, 2 showed asymmetrical filling in addition to oligemia, and 1 showed only asymmetrical filling. Filling defects, cutoffs, and pruning did not occur in any of the patients who clinically did not have pulmonary embolism.

Discussion

It might be thought that the only truly reliable method of establishing criteria

*Left ventricular end-diastolic pressure was 23 mm. Hg.

Table II. All patients with pulmonary angiograms

	Angiogram	
	Abnormal	Normal
Clinically pulmonary embolism	24/29 (83%)	5/29 (17%)
Clinically no pulmonary embolism	7/23 (30%)	16/23 (70%)

*Table IV. Clinically uncomplicated patients**

	Angiogram	
	Abnormal	Normal
Clinically pulmonary embolism	20/21 (95%)	1/21 (5%)
Clinically no pulmonary embolism	1/6 (17%)	5/6 (83%)

*No concurrent cardiac or pulmonary diseases that affect the pulmonary vasculature.

Table III. All patients with pulmonary angiograms

	Clinically pulmonary embolism	Clinically no pulmonary embolism
Filling defects	19/29	0/23
Cutoffs	11/29	0/23
Pruning	16/29	0/23
Oligemia	12/29	5/23
Asymmetrical filling	10/29	5/23
Prolonged arterial phase	10/29	2/23
Bilateral lower zone filling delay	4/29	2/23

*Table V. Clinically uncomplicated patients**

	Clinically pulmonary embolism	Clinically no pulmonary embolism
Filling defects	15/21	0/6
Cutoff	11/21	0/6
Pruning	13/21	0/6
Oligemia	10/21	0/6
Asymmetrical filling	8/21	1/6
Prolonged arterial phase	10/21	1/6
Bilateral lower zone filling delay	4/21	0/6

*No concurrent cardiac or pulmonary diseases that affect the pulmonary vasculature.

of pulmonary embolism angiographically would be by comparison of angiographic findings premortem with pathologic findings and arteriograms postmortem. Unfortunately, this is almost impossible to do except experimentally, as we have done, in which case dogs or other species are used and the animal has essentially normal lungs. In patients, there is usually a lapse of time between the performance of pulmonary angiography and death during which time emboli may have lysed or further embolism may have taken place. Thus, one is forced to make such studies in man

as done here by performing pulmonary angiography in patients in whom the diagnosis of embolism appears to be unquestionable and in whom the controls appear unquestionably not to have suffered embolization We recognize the difficulties involved in this respect but in this report we have made every effort to keep clear these two divisions of patient material Where doubt existed the findings have been omitted from this report.

A wide variety of abnormalities have been described in the pulmonary angiograms of patients with pulmonary embolism and in the pulmonary angiograms of patients with other diseases. Some of the angiographic abnormalities are specific for pulmonary embolism and some are not specific Prior to this study no attempt has been made to quantify by empirical methods the reliability of each of the previously described angiographic abnormalities, in order to determine which signs or group of signs are valid for the diagnosis of pulmonary embolism irrespective of coexistent diseases that can affect the pulmonary vasculature

The angiographic appearance of the normal pulmonary circulation has been adequately described by others [1-11] Symmetry of flow and other analogous aspects of the angiographic appearance have been confirmed in our animal laboratory In a normal patient (Fig 6) after an injection of contrast material into the outflow tract of the right ventricle or the proximal portion of the main pulmonary artery all lobes of the lung fill simultaneously and empty simultaneously There is uniform distribution of contrast material All pulmonary arterial branches are well defined taper gradually and divide into numerous fine branches. Except for the central portions, they follow closely the bronchial ramifications.

The first attempt to investigate the appearance of the pulmonary vasculature in the presence of pulmonary embolism was made by Jesser and deTakáts in 1941 [12] They described a reduction of the size of the pulmonary arterial tree and blocked main vessels after embolization of the pulmonary artery of dogs with barium sulfate suspension The absence of filling of the pulmonary artery beyond the site of occlusion was also observed by



Fig 6 Normal pulmonary angiogram All zones have filled simultaneously and will empty simultaneously There is uniform distribution of contrast material. All pulmonary arterial branches are well defined taper gradually and divide into numerous fine branches.

Liberson and Liberson[11] in 1942 in pulmonary angiograms taken after the injection into rabbits of lead filings mixed with paraffin. The intraluminal filling defect, the direct shadow picture of an embolic mass, was first described in pulmonary embolism by Lochhead, Roberts, and Dotter[14] in 1952 after they performed venous angiography in 6 dogs embolized with autologous blood clots. They also described incomplete occlusion of vessels, reduced rate of flow through the region of the clot, diminished opacification of distal vessels, and dilatation of the pulmonary artery proximal to the embolus.

Chrispin, Goodwin, and Steiner, in 1963 performed angiography (some right atrial and some pulmonary arterial injections) in 7 patients with clinical evidence of pulmonary embolism. They categorized angiographic signs into those of major artery occlusion and those of peripheral vessel occlusion. Obstruction of major arteries seemed to be associated with a reduced number of peripheral branches, areas of increased transradiency (oligemia), slow passage of contrast material into the capillaries (asymmetrical filling), and failure of the pulmonary veins to fill. Obstruction of smaller vessels was associated with slow disappearance of contrast material from the arteries (prolonged arterial phase), peripheral pruning, and tortuous vessels.

Williams and associates, in 1963, in addition to previous observations, reported narrowing and irregularity of opacified vessels which they attributed to circumferential organization of thromboemboli.

Smith, Dammin, and Dexter,[4] utilizing postmortem arteriography, illustrated reduced opacification of small vessels in the periphery of the lung when small vessels were embolized. Sasahara and associates[4] mentioned plaque-like filling defects among the angiographic abnormalities noted in patients with clinical evidence of pulmonary embolism. They noted difficulty of interpretation in patients with mitral stenosis or chronic lung disease. Dalen and colleagues,[19,21] in this laboratory, recorded 280 selective pulmonary angiograms in 23 dogs embolized with autologous clots (17 dogs with radiopaque autologous clots) and observed cutoffs, areas of oligemia, and filling defects to be typical angiographic abnormalities due to embolization. The value of utilization of angiographic signs in addition to filling defects was illustrated in some cases by contrast material passing around a partially occluding embolus in quantities sufficient to prohibit visualization of the embolus itself.

The results of this study indicate that it is useful to divide angiographic signs into two groups: those of major or morphologic significance, and those of lesser or physiologic validity. The first group is composed of intraluminal filling defects of various sizes, shapes, and locations, abrupt cutoff of an artery, and localized pruning, i.e., lack of branching. The second group consists of oligemia, asymmetrical filling, prolongation of the arterial phase, and bilateral lower zone filling delay. All of these angiographic signs correspond well to those observed in this laboratory after experimental embolization in dogs.[9] Of the 21 patients in this study who clinically had pulmonary embolism without known coexistent pulmonary disease, mitral stenosis, or left ventricular failure, 20 patients (95 per cent) showed various combinations of these major or lesser angiographic signs (Tables IV and V). The signs of physiologic significance were particularly useful in calling attention to some of the angiograms in which the changes due to pulmonary embolism were subtle.

Only signs of morphologic significance were reliable for the diagnosis of pulmonary embolism in patients with coexistent diseases that can affect the pulmonary vasculature. Cardiac diseases[29-32] and pulmonary diseases[1,33-36] other than pulmonary embolism can alter the pulmonary vasculature and therefore affect the pulmonary blood flow. Such changes in flow would produce the lesser angiographic abnormalities, those of physiologic significance. Generalized emphysema, localized emphysematous bullae, and other chronic conditions may cause generalized or localized hypoperfusion (oligemia) and some of the other angiographic signs of secondary importance.[33] Mitral stenosis with pulmonary hypertension[29] and other cardiac diseases with postcapillary hypertension, such as left ventricular failure,[31] are likely to cause lower zone filling delay. Thus signs

significant in an otherwise healthy lung such as underperfusion of the lower zones, would have no diagnostic significance as to acute pulmonary embolism in a patient with mitral stenosis and pulmonary hypertension. Therefore in patients with preexisting conditions that can affect the pulmonary vasculature one can rely upon the direct visualization of the embolus (the intraluminal filling defect) the obstruction of an artery (cutoff) or the nonfilling of smaller branches in a circumscribed area (pruning). Utilization of filling defects cutoffs and pruning as angiographic signs of pulmonary embolism only somewhat reduced the number of positive angiograms from 83 to 79 per cent in patients who clinically had pulmonary embolism (Table VI). Furthermore utilization of these angiographic criteria for pulmonary embolism eliminated all false positive interpretations.

It is apparent that there is a wide variety of angiographic signs of acute pulmonary embolism. They depend on the variegated pathologic happenings such as the size and number of emboli on their central or peripheral location and whether they obstruct completely or only partially. When only the signs of morphologic significance were used a good correlation was made in this study between the clinical diagnosis of acute pulmonary embolism and the angiographic diagnosis irrespective of coexistent cardiopulmonary diseases. The signs of physiologic significance interpreted in an otherwise normal lung

Table VI. All patients with pulmonary angiograms

	Filling defects cutoff pruning	No filling defects cutoff pruning
Clinically pulmonary embolism	$\frac{23}{29}$ (79%)	$\frac{6}{29}$ (21%)
Clinically no pulmonary embolism	$\frac{0}{23}$ (0%)	$\frac{23}{23}$ (100%)

also have great diagnostic value but must be interpreted with caution in patients with a wide variety of pulmonary diseases.

Our present experience recommends selective pulmonary angiography as a valuable diagnostic procedure. In many instances it is of absolute reliability. Proper evaluation of the angiographic abnormalities with consideration of coexistent diseases that affect pulmonary blood flow increases the accuracy of the angiographic diagnosis of pulmonary embolism. Utilization of the angiographic signs of morphologic significance enables the diagnosis of acute pulmonary embolism to be reliable even in the presence of other diseases affecting the pulmonary vasculature. Utilization in addition of the signs of physiologic significance facilitates recognition of subtle changes due to pulmonary embolism in an otherwise healthy lung.

Summary

Abnormalities in the pulmonary angiograms of 52 patients were correlated with the clinical diagnoses in order to determine which angiographic signs are diagnostic of acute pulmonary embolism and which are abnormal but possibly related to other diseases affecting the pulmonary vasculature.

Angiographic abnormalities were divided into two groups: those of major or morphologic significance and those of lesser or physiologic significance. The signs of morphologic significance are intraluminal filling defects, cutoffs, and pruning. These major signs directly indicate arterial occlusion. The signs of physiologic significance are oligemia, asymmetrical filling, prolongation of the arterial phase, and bilateral lower zone filling delay. These lesser signs indicate disturbance of flow. In an otherwise normal lung, they are highly suggestive of pulmonary embolism. In the presence of coexistent diseases that affect the pulmonary vasculature, correlations in this study show that only the signs of morphologic significance are reliable for the diagnosis of acute pulmonary embolism. In otherwise healthy patients, 95 per cent (20 of 21) who clinically had pulmonary embolism had one or more of the major or lesser angiographic abnormalities. In the entire group who clinically had pulmonary

embolism (including patients with coexisting diseases that affect the pulmonary vasculature) 83 per cent (24 of 29) of the patients had one or more of the major or lesser angiographic abnormalities. However 7 patients with nonembolic pulmonary vascular disease had lesser angiographic abnormalities (disturbance of flow). Utilization of the major signs alone reduced the number of positive angiographic interpretations to 79 per cent (23 of 29) in patients who clinically had pulmonary embolism but eliminated all false positive interpretations. Accuracy in making the diagnosis of acute pulmonary embolism by pulmonary angiography is enhanced by proper evaluation of the angiographic abnormalities of morphologic and physiologic significance as described in this study.

REFERENCES

1. Angiography in pulmonary embolism, (leading article) Lancet 2:923, 1963.
2. Cooley, R. N.: Pulmonary thromboembolism—the case for the pulmonary angiogram, Am. J. Roentgenol. 92:693, 1964.
3. Littman, D.: Pulmonary angiography, Am. Heart J. 69:569, 1965.
4. Sasahara, A. A., Stein, M., Simon, M., and Littmann, D.: Pulmonary angiography in the diagnosis of thromboembolic disease, New England J. Med. 270:1075, 1964.
5. Dexter, L., Dock, D. S., McGuire, L. B., Hyland, J. W., and Haynes, F. W.: Pulmonary embolism, M. Clin. North America 44:1251, 1960.
6. Kinsey, D., and White, P. D.: Fever in congestive heart failure, Arch. Int. Med. 65:163, 1940.
7. Moran, T. J.: Autopsy incidence of pulmonary embolism in coronary heart disease, Ann. Int. Med. 32:949, 1950.
8. Wennevold, A., Christiansen, I., and Lindeneg, O.: Complications in 4,413 catheterizations of the right side of the heart, Am. Heart J. 69:173, 1965.
9. Bagger, M., et al.: On methods and complications in catheterization of the heart and large vessels, with and without contrast injection, Am. Heart J. 54:766, 1957.
10. Dalen, J. E., Mathur, V. S., Evans, H., Haynes, F. W., Pur-Shahriari, A. A., Stein, P. D., and Dexter, L.: Pulmonary angiography in experimental pulmonary embolism, Am. Heart J. 72:509, 1966.
11. Dotter, C. T.: The normal pulmonary arteriogram, *in* Abrams, H. L., editor: Angiography, Boston, 1961, Little, Brown and Company, Vol. I, p. 301.
12. Simon, M., and Sasahara, A. A.: Observations on the angiographic changes in pulmonary thromboembolism, *in* Sasahara, A. A., and Stein, M., editors: Pulmonary embolic disease, New York, 1965, Grune & Stratton, Inc., p. 214.
13. Jesser, J. H., and deTakáts, G.: Visualization of the pulmonary artery during its embolic obstruction, Arch. Surg. 42:1034, 1941.
14. Liberson, F., and Liberson, I. R.: The use of Diodrast in determining the location and extent of pulmonary embolism. An experimental study, Am. J. Roentgenol. 48:352, 1942.
15. Lochhead, R. P., Roberts, D. J., Jr., and Dotter, C. T.: Pulmonary embolism, experimental and angiocardiographic study, Am. J. Roentgenol. 68:627, 1952.
16. Chrispin, A. R., Goodwin, J. F., and Steiner, R. E.: The radiology of obliterative pulmonary hypertension and thromboembolism, Brit. J. Radiol. 36:705, 1963.
17. Williams, J. R., Wilcox, C., Andrews, G. J., and Burns, R. R.: Angiography in pulmonary embolism, J.A.M.A. 184:473, 1963.
18. Smith, G. T., Dammin, G. J., and Dexter, L.: Postmortem arteriographic studies of the human lung in pulmonary embolization, J.A.M.A. 188:143, 1964.
19. Dalen, J. E., Mathur, V., Haynes, F. W., Evans, H., Shahriari, A., Stein, P., and Dexter, L.: Radiopaque pulmonary embolism, (Abstract) Clin. Res. 13:204, 1965.
20. Goodwin, J. F., Stein, R. E., and Lowe, K. G.: The pulmonary arteries in mitral stenosis demonstrated by angiocardiography, J. Fac. Radiologists 4:21, 1952.
21. Simon, M.: The pulmonary vessels in incipient left ventricular decompensation, radiologic observations, Circulation 24:185, 1961.
22. Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs of mitral stenosis, Am. J. Path. 12:573, 1936.
23. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man, Am. J. Roentgenol. 41:1, 1939.
24. Harris, P., and Heath, D.: The human pulmonary circulation, its form and function in health and disease, Baltimore, 1962, Williams & Wilkins Company, p. 276.
25. Harris and Heath, p. 151.

Deformed anterior mitral valve leaflet without mitral insufficiency in persistent common atrioventricular canal

Anatomic and angiocardiographic correlations

Zwi Schlesinger, M.D.
Victor Deutsch, M.D.
Joseph H. Yahini, M.D.
Henry N. Neufeld, M.D.
Tel-Aviv, Israel

The complex of congenital cardiac malformations described as persistent common atrioventricular canal or endocardial cushion defects is the result of abnormalities in the growth and fusion of the endocardial cushions in the embryonic heart.[1]

These defects are comparatively rare and account for 1.7 per cent of congenital cardiac malformations.[2] Interest in them arises mainly from the challenge that they present in differential diagnosis,[3-4] and from the surgical problems that are involved in the repair of them.

Because of the complexity of the malformations,[5-8] diagnosis of the basic anatomic abnormalities is often difficult to make on the basis of the history and physical findings alone.[3] The electrocardiogram and vectorcardiogram may provide considerable information[19-22] but do not indicate the extent of the anatomic abnormalities. Data provided by cardiac catheterization and dye-dilution curves help in demonstrating the altered hemodynamics of the lesion but fail to reveal the basic anatomic abnormalities,[17,21] which are best demonstrated by angiocardiography.[17] An integral part of the anatomic malformation in this anomaly is the deformity of the anterior leaflet of the mitral valve, which is almost always cleft and usually allows a variable degree of leakage.[25] Assessment of this leakage is of major importance in an evaluation of the severity of the lesion,[18] since both the prognosis and the surgical approach and outcome depend to a large extent on the degree of the mitral insufficiency.[18] The latter cannot always be assessed by clinical means[18] or by direct exploration of the valve during open heart operation or at postmortem examination.[19,27]

The purpose of this report is to emphasize that some cases of persistent common atrioventricular canal are not accompanied by mitral insufficiency, despite the presence of a markedly deformed and cleft anterior mitral valve leaflet. Four cases are presented in which the presence of a

From the Heart Institute and Department of Radiology, Tel-Hashomer Government Hospital, University of Tel-Aviv Medical School, Tel-Aviv, Israel.
Received for publication July 13, 1966.
Address: Heart Institute, Tel-Hashomer Government Hospital, Tel-Aviv, Israel.

cleft and deformed anterior mitral valve leaflet was demonstrated by angiocardiography with surgical and postmortem confirmation in three but in which no evidence of mitral valve leakage was detected by selective left ventriculography

Anatomic and angiocardiographic considerations

In the normal heart the anterior mitral valve leaflet arises from an annulus which is common to the aortic and mitral valves. It is attached only for a short distance to the posterior border of the atrioventricular septum and moves freely in the ventricular cavity In the left ventriculogram the opacification of the anteriorly placed left ventricular outflow tract, which overlaps the anterior mitral valve area both in systole and diastole explains why the line of attachment of the anterior leaflet cannot normally be visualized The region of the left ventricular outflow tract situated between the anterior mitral valve leaflet and the aortic orifice gives a smooth filling image that is continuous with the cavity of the left ventricle (Fig 1)



Fig 1 A normal left ventriculogram, left anterior oblique view [illegible] case of atrial septal defect of the secundum type The catheter was inserted into the femoral artery and advanced in retrograde fashion into the left ventricle. Note that the outflow tract is smooth, and outlined sharply

Normally the mitral valve opens into the posterior portion of the left ventricle immediately below the aortic valve. This opening can be identified in the left ventriculogram as a filling defect produced by the diluting effect of the blood of the non opacified left atrium rushing into the left ventricle This is best seen during the rapid filling phase of diastole

The posterior mitral valve leaflet is attached to the mitral annulus along the junction of the left atrium and ventricle The inrush of blood from the nonopacified left atrium demarcates the border of attachment of the posterior leaflet by a line of contrast in the left ventricular opacification best seen during early diastole in the frontal ventriculogram This line of demarcation results from the contrast material being trapped in the recess between the posterior mitral valve leaflet and the posterior wall of the left ventricle.

The anatomic alterations in the ventricular cavity in persistent common atrioventricular canal result primarily from two factors (a) the deformation and displacement of the anterior mitral valve leaflet, along with its papillary muscle and chordae and (b) the impingement of this leaflet and its abnormal papillary muscle and chordae on the left ventricular outflow tract with resultant narrowing and elongation of the tract. The angiocardiographic features of the persistent common atrioventricular canal have been recently described by Baron and associates[1] and others,[2-9] and are based mainly on these two anatomic alterations.

Regardless of the severity of the anomaly the mitral valve is cleft in almost all cases. In the angiocardiogram the cleft is seen during diastole (Figs. 2 and 3 *B*) when the two halves of the anterior mitral valve leaflet separate widely by swinging into the ventricular cavity in such a way that the superior part bulges into the left ventricular outflow tract and the inferior part moves toward the septum The bulging of the superior part results in the narrowing of the left ventricular outflow tract, which is well seen on left ventriculography in the frontal plane as a gooseneck deformity[10] (Figs. 2 and 4,*A*) The movement of the inferior part traps contrast material against the septum so that



Fig. 2 Case 2. Left ventriculogram trans-septal approach frontal view diastolic phase in case of partial form of persistent common atrioventricular canal with left mitral valve and small left ventricular right atrial communication. The cleft anterior mitral valve leaflet is seen. The superior part (upper arrow) of the cleft bulges into the left ventricular outflow tract causing its narrowing (gooseneck), and the inferior part (lower arrow) moves toward the septum. The mitral insufficiency in this approach was most probably artifactual and caused by the catheter (see text and Fig. 5).

this part of the leaflet is delineated. Although the narrowing of the left ventricular outflow tract can also be recognized in systole the cleft and the displacement of the anterior mitral leaflet are obscured since the ventricle is evenly opacified. The presence of significant mitral insufficiency causes opacification of the left atrium and results in the superimposition of contrast material in the region of the cleft so that the latter cannot be recognized even in diastole.

In the persistent common atrioventricular canal type of abnormality the mitral ring is displaced anteriorly downward and to the right. On ventriculography in the lateral position it will therefore be seen practically *en face* whereas normally in this position it is seen obliquely. The displacement of the mitral opening is also well visualized on left ventriculography (Figs. 2 and 3 B).

The abnormal attachment of the cleft anterior mitral valve leaflet to the septum is almost always present in cases of persistent common atrioventricular canal. This septal area of attachment is usually deficient of substance because of the basic abnormal embryologic development and an interventricular communication might be present in this area.

We have found that on left ventriculography the anterior left oblique view is optimal in demonstrating the abnormal attachment of the anterior leaflet of the cleft mitral valve to the septum. The abnormal attachment is located in the anteromedial part of the left ventricular outflow tract and appears on the left ventriculogram as a markedly irregular and scalloped contour of the tract (Figs. 3, 5 and 6).

Case reports

Case 1. O. S. 15-year-old boy was known to have had heart murmur since birth and to have suffered from dyspnea and palpitations on mild exertion. He was mentally retarded and had shown signs of kernicterus in infancy.

Physical examination revealed a noncyanotic Mongoloid male. There were no signs of heart failure. The blood pressure was 120/80 mm. Hg, and the pulse rate was 80 per minute and regular. Palpation of the heart was difficult on account of a marked deformity of the left side of the chest. A Grade 2/6 ejection systolic murmur was heard at the pulmonic area. The second sound at the pulmonic area was widely split and fixed on respiration. The pulmonic component was somewhat increased. There was no apical murmur. The electrocardiogram showed a mean manifest electrical axis of the QRS complex of −30 degrees in the frontal plane, with the frontal vectors directed counterclockwise and RR pattern in Lead V. The chest roentgenogram revealed increased vascularity of the lungs, suggestive of left-to-right shunt, prominence of the main pulmonary artery segment, and slight cardiomegaly. There were no signs of enlargement of the left atrium.

Right heart catheterization (February 1966) revealed a marked left-to-right shunt at the atrial level and high normal pressures in the right ventricle and pulmonary artery with normal pulmonary resistance. Selective retrograde left ventriculography (February 1966) revealed (Fig. 6) a small left-to-right shunt at the ventricular level. The characteristic deformities of the membranous ventricular septum due to the abnormally attached anterior mitral valve leaflet and the deformed left ventricular outflow tract were present. There was no evidence of mitral insufficiency.

The patient died of complications after open-heart operation during which a patch was inserted to repair the interatrial defect. No attempt was



Fig 3 Case 4 A Retrograde left ventriculogram anterior left oblique view systolic phase in case of persistent common trioventricular canal, ostium primum type. The bnormal ttachments of the cleft terior mitral alv leaflet to the septum are demonstrated by the typical irregularity of the septal portion of the left entricular outflow tract (rrow) B Diastolic phase. The mitral lve opening is displaced, and the left m ts anterior leaflet (arrow) and its abnormal ttachments to the septum are shown. Not that no mitr l insufficiency is present (A and B).



Fig 4 Case 3 Lef en ric logram transeptal pproach in case of pe sistent ommon atrioven ricular anal ostium primum pe l leon l iew systolic phase showing the narrow ng and dis ortion of the left en tricular outflow tract (gr oseneck) Not the filling defect in the righ pper portion of he left entricle (arrow) caused by he abnormally placed erior papillary muscle. B La eral iew The terior spect of the left entricular outflow tract is irregularly scalloped (black arrow) The filling defect mentioned bov is seen (white arrow). There is slight opac fica ion of the right entricle caused by the small i terventricular communic tion (arrows).

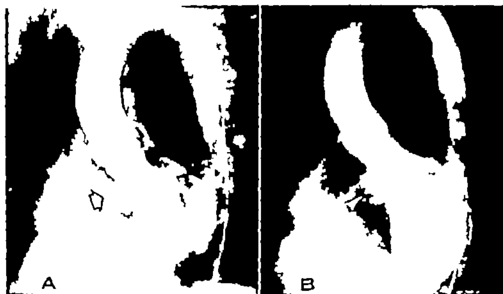


Fig 5 Case 2 Retrograde left entriculogram left a terior oblique iew A Systolic phase, B Diastolic phase Both A and B show irregularity of the left entricular outflow tract at its septal portion (rrow) and slight opacification of the right trum and right entricle due to left entricular right atrial communication. N mitral insufficiency is present (see also F g 2).



Fig 6 Case 1 Retrograde left entriculogram, anterior left oblique view in case of partial form of persistent common trioventric lar canal, ostium primum type The upper portion of the ventricular septum below the aortic cusp is irregularly scalloped, because of abnormal attachment of the cleft terior mitral valve leaflet to the septum The right ventricle is slightly opacified because of multiple small terventricular communications in this rea. There is no evidence of mitral insufficiency

made t repair the cleft mitral v h since no mitral insufficiency was evident prior to operation. Necropsy revealed (Fig 7 A nd B) large atrial septal defect of the persistent common trioventricular canal type there was left he markedly deformed anterior leaflet of the mitral valve hich was displaced teriorly nd to the right and showed bnormal ttachment of the hordea. On close exam nation the rea of the septum to hich the bnormal anterior mitral valv leaflet was attached showed lack of tissue and few small perforations, which explained the mild left-to-right shunt seen on the left entriculogram (Fig 6).

COMMENT This was case of a partial form of persistent common trioventricular canal defect with marked deformity of the anterior mitral alv leaflet demonstrated by left entriculography and confirmed by topsy Left entriculography performed before operation did not reveal any sign of mitral incompetence despite th presence of the markedly deformed mitral alv leaflet.

Case 2 A.L. a 49-year-old ma was known to be suffering from congenital heart disease. His main complaint was fatigability on trenuou physical exertion Examination revealed slight right entricular hea Grade 2/6 ejection systolic murmur best heard t the pulmonic area and Grade 1/6 pical blowing sy tolic murmur transmitted t the left xilla. The second sound t the pulmonic area was split on respiration. The blood pressure was 125/75 mm. Hg, nd the heart rate was 70 per minut and regula The electrocardiogram (Fig 8) revealed mean manifest lectrical axis of the QRS complex of −50 degrees i the frontal plane ith the frontal vectors directed counterclock ise and



Fig 7 Case 1 Necropsy specimen. A The heart has been opened to show the markedly deformed and cleft anterior mitral valv leaflet (rrow). The trial septal defect is low nd closed by patch B The same heart show the abnormal hordal ttachment of the nterior mitral valv leaflet to the septum (arrows), where there is deficiency of septal substance with few very small interventricular communications. This area was visualized learly in the left entriculogram (see Fig 4)

incomplete right bundle branch block. The best roentgenogram revealed slight cardiomegaly due to enlargement of the right entricle the pulmonary artery segment was slightly prominent, and the pulmonary ascularity was somewhat increased

Cardiac catheterization, performed through the right femoral el (October 1963), disclosed normal pressures in the hambers of the right side of the heart and in the pulmonary artery The catheter passed from the right to the left trium through an interatrial communication and then to the left entricle where the injected contrast m terial revealed the presence of moderate mitral insufficiency (Fig 2). Left entriculography was repeated by the retrograde pproach through the left femoral artery and f iled t demonstrat any degree of mitral regurgitation (Fig 3, A and B). The conclusion was that the mitral insufficiency that had been detected by the previous transeptal left entriculography had probably been produced by the location of the catheter in the cleft mitral alve leaflet hich resulted in mechanical interference ith the mobility of this leaflet Both entriculograms demonstrated the typical deform ty and abnormal position of the terior mitral leaflet and the distortion of the left entricular outflow tract (Figs. 2 and 3).

COMMENT This was case of partial form of persistent common trioventricular canal defect with cleft mitral alv demonstrated by left entriculography Again, there was no evidence of mitral regurgitation, despit the markedly deformed nterior mitral leaflet

Case 3 M B 32 year-old woman, was known to have had heart murmur since the age of 14 For the past 4 years she had complained of shortness of breath and palpitations on marked exertion There as no history of congesti heart failure The pulse rate was 80 per minute nd regular and the blood pressure as 130/70 mm Hg There was marked right entricular hea e. A Grade 2/6 ejection systolic murmur was heard t the pulmonic area, and blowing Grade 1/6 systolic murmur at the pex. The second pulmonic sound was split nd fixed the pulmonic component as somewhat accentuated The electrocardiographic findings ere suggestive of persistent common trioventricular canal The chest roentgenogram revealed increased pulmonary ascularity with pattern of left-to-right shu t There was slight cardiomegaly ith bulging of the main pulmonary artery segment. The left trium and entricle ere not enlarged.

Right heart catheterization (November 1961) revealed left-to-righ shunt t the trial level, ith normal pressures i the right ventricle nd pulmonary artery

Selectiv lef entriculography was performed in February 1964 (Fig 4). The catheter was introduced through the right femoral vein and passed through trial septal defect into the left trium and lef entricle. Minimal mitral insufficiency as detected A small left-to-righ shu t was present i the region of attachment of the bnormal chordae of the anterior mitral alv leaflet t the tricular septum. The goose-neck d left entricula outflow tract (Fig 4)

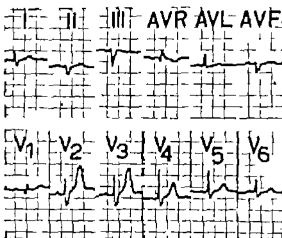


Fig 8 Case 2 Electrocard gram hows ng sinus rhythm P R interval of 0 11 second The mea man fest electric l QRS is in the frontal plane is −50 degrees Incomplet right bundle branch block The t acing is haracterist of persistent ommon triov entric lar nal

formed terior m tral h le flet nd the displaced terior papillary m scle were w ll hurbred (F g 4 1 nd B)

Surgic l tervention as directed toward losure of the teratrial septal defect ithout y ttempt t repair of the m tral left The patient died i the arly postoperat period nd necropsy revealed (Fig 9) the typical left terior mitral al leaflet w th t deformed bordae nd abnormally located papillary muscle The terior leaflet was ttached an bnormal y to the sept m where tissue deficiency as present, and some small i terventricular omm ucations could be found on close examination The tricuspid h was unaffected. The i teratrial defect was large i size

COMMENT This as case of partial form of persistent common triov entricula canal defect with markedly deformed mitral al and with cleft anterior leaflet detected on left entriculog raphy nd confirmed t topsy As i Case 2 the minimal signs of m tral regurgitation seen on left entriculography were probably due t mechanical i terference t the movement of the m tral valve caused by the catheter

Case 4 C.S 39-year-old woman was known t ha e had heart murmur since childhood. For the past 6 years she had complained of shortness of breath and palpitations on moderate exertion Physical exam nation revealed somewhat over weight woma in good general condition Th pulse rate was 85 per min te and regular nd the blood pressure was 125/85 mm. Hg A mild right entricular heave was present. A Grade 3/6 ejection systolic murmu was heard t the pulmonic area, with wide splitting of the second sound nd slightly accentuated pulmonic component pical murmur was detected. The electrocardiogram showed a mean manifest electrical axis of the QRS complex of −40 degrees in the frontal plane w th frontal ectors d rected cou terclockwise, nd a RR pat tern I Le d V The chest roentgenogram revealed increased pulmonary asculrity suggestive of left to-right shu t nd prominence of the main pulmonary artery segment with slight cardiomegaly There was no evidence of enlargement of the left tri m. Right heart catheterization (October 1964) revealed a left to-right shunt t the atrial level, with high normal right entricular nd pulmonary rterial pressures. Selectiv left entriculography performed (February 1965) through the aortic pproach (Fig 3) demonstrated normal-sized left entricle without evidence of mitral insuffi ciency or of shu t t the entricula level. The cleft i the terior mitral valve leaflet (Fig 3,B) nd the presence of its abnormal ttachments to the membranous septum was well demonstrated by the haracteristic picture i the left a terior oblique view (Fig 3).



Fig 9 Case 3 Necropsy specimen The heart has been opened to show the cleft and deformed anterior leaflet of the mitral val (*hite arrow*), causing the narrowi g of the left entricular out flow tract (*se F g 4 1*) The abnormal attachments of the anterior leaflet of the mitral valve to the septum are shown (*bl k arrow*). This septal area is deficient in substance and as well visualized in the lateral left entriculogram (*see Fig 4,B*). The nterior papillary muscle (*P*), which is thick and displaced caused the filling defect seen in the ventriculogram (*see Fig 4,A nd B*).

The patient was operated on, and the atrial septal defect repaired with a patch. The anterior leaflet of the mitral valve was found to be deformed and cleft but again no attempt was made to repair the cleft mitral valve since there were no signs of mitral insufficiency prior to operation. Examination after the operation did not reveal any signs of atrial septal defect or of mitral insufficiency.

COMMENT: This was another example of the partial form of persistent common atrioventricular canal defect, with the typical angiocardiographic features of a markedly deformed and cleft anterior mitral valve leaflet, but without evidence of concomitant mitral insufficiency.

Discussion

Recent experience with cases of persistent common atrioventricular canal type of abnormalities has shown that the clinical findings and hemodynamic data may be misleading in so far as the assessment of the concomitant mitral insufficiency is concerned.[11,20-22] Palpation of the apical impulse may reveal a heave, an apical systolic murmur "typical" of pronounced mitral insufficiency may be heard, and yet no evidence of mitral insufficiency may be found.[1] This is well illustrated in our second case. The misleading clinical signs may be due to the presence of marked clockwise rotation producing an apical heave due to right ventricular enlargement and to the interpretation of murmurs of tricuspid or pulmonic origin as being of mitral origin.[17]

The electrocardiogram with its characteristic left axis deviation and counterclockwise rotation, typical of persistent common atrioventricular canal,[1-22] bears no relationship to the existence or severity of the mitral insufficiency in these cases. The estimation of cardiac and/or left atrial size from the plain roentgenograms is likewise of limited value in determining the presence of associated mitral insufficiency.[11,23,24] Furthermore, it is almost impossible to detect the presence or to evaluate the degree of mitral insufficiency even during open-heart operation while the heart is "contracting dry." The postmortem examination will reveal the details of the basic anatomic abnormalities but may not enable one to assess the competence of the mitral valve,[15] as in Cases 1 and 3. The method of choice for the assessment and evaluation of the mitral insufficiency is therefore selective left ventriculography.[11,17,2,23,24] The point to be stressed is that it is imperative to assess the degree of mitral insufficiency peroperatively since this determines the prognosis and the surgical approach and outcome.[17]

As shown in this report, there are cases of persistent common atrioventricular canal type of defect with a cleft and deformed mitral valve with characteristic distortion and thickening of the anterior mitral valve leaflet and its chordae tendineae, with displacement of the anterior papillary muscle and with abnormal attachment of the cusp and chordae to the membranous septum and yet without evidence of mitral insufficiency. That there was no mitral valve leakage in these cases was proved by selective left ventriculography.

It is known that certain of the chordae tendineae in the persistent common atrioventricular canal type of abnormalities do not have a counterpart in the normal heart; the surgical closure of the cleft and the retention of some of those accessory chordae may interfere with the normal mobility of the valve and result in considerable postoperative mitral insufficiency.[11] The question arises, therefore, whether one should not refrain from trying to repair a deformed and/or cleft mitral valve in cases in which the preoperative left ventriculogram has shown no evidence of mitral valve leakage.

In our experience, left ventriculography in these cases should be performed through the retrograde aortic approach. This eliminates artificially induced mitral insufficiency produced by the catheter wedged between the halves of the cleft mitral valve leaflet when the transseptal approach is used (Cases 2 and 3). It should also be stressed that, although most details can be seen in the anteroposterior and lateral views,[1] we have found that the left anterior oblique position (Figs. 3, 5, and 6) best demonstrates the characteristic abnormal attachment of the anterior mitral leaflet to the ventricular septum since the abnormal attachments are located in the anteromedial part of the left ventricular outflow tract.

Pitfalls in the angiocardiographic diagnosis may arise when the blood in the nonopacified left atrium produces a filling defect in diastole in the normal year



Fig. 10 Left ventriculogram anterior left oblique view of patient with ventricular septal defect after surgical closure with residual left-to-right shunt. The catheter was introduced into the left atrium by the transseptal route and the contrast material was injected into the left appendage. *A* Systolic phase. Marked irregularity of the upper portion of the membranous septum (*arrow*) due to residual left-to-right shunt which mimics the appearance of septal distortion seen in persistent common atrioventricular canal. *B* Diastolic phase. Note that the mitral valve ring is located normally and that the septal distortion is no longer apparent.

thus mimicking the features of persistent common atrioventricular canal type of abnormalities[17] the lack of constancy of this defect in subsequent cycles clarifies the situation however.

The presence of a small high ventricular septal defect with left-to-right shunt may produce in the lateral and left anterior oblique positions, a picture in the region of the upper part of the septum[17,41] similar to that described for persistent common atrioventricular canal type of abnormalities (Fig. 10). The differentiation becomes easy however when one pays attention to the lack of a gooseneck deformity and the normally located mitral valve ring in the left ventriculogram of the ventricular septal defect.

Summary

The basic anatomic features of persistent common atrioventricular canal are reviewed and correlated with the angiocardiographic features of this anomaly.

It is emphasized that selective left ventriculography is the method of choice for diagnosing and assessing the severity of the malformations and that the left anterior oblique position best delineates the characteristic abnormal attachment of the anterior mitral valve leaflet to the septum.

The importance of the preoperative assessment of the mitral insufficiency is stressed and the difficulties encountered in the diagnosis of it are outlined.

Four cases are presented in which selective left ventriculography revealed no evidence of mitral incompetence, despite the presence of a markedly deformed and distorted anterior mitral valve leaflet.

Left ventriculography by the transseptal approach may interfere with the mobility of the mitral valve leaflet and may produce an artifactual mitral insufficiency. This may be avoided by using the aortic retrograde approach.

It is suggested that in the absence of mitral incompetence repair of the mitral cleft should be avoided since it may hamper the operative results.

REFERENCES

1. Kramer, T. C.: Partitioning of truncus and conus and formation of membranous portion of interventricular septum in human heart, Am. J. Anat. 71:343, 1942.
2. Wakai, C. S., and Edwards, J. E.: Developmental and pathologic considerations in persistent common atrioventricular canal, Proc. Staff Meet. Mayo Clin. 31:487, 1956.

3. Van Mierop, L. H. S., Alley, R. D., Kausel, H. W., and Stranahan, A.: The anatomy and embryology of endocardial cushion defects, J. Thorac. & Cardiovas. Surg. 53:71, 1962.
4. Rogers, H. M., and Edwards, J. E.: Incomplete division of the atrioventricular canal with patent interarterial foramen primum. Report of five cases and review of the literature, Am. Heart J. 36:28, 1948.
5. Campbell, M., and Missen, G. A. K.: Endocardial cushion defects. Common atrioventricular canal and ostium primum, Brit. Heart J. 19:403, 1957.
6. Wakai, C. S., and Edwards, J. E.: Pathologic study of persistent common atrioventricular canal, Am. Heart J. 56:779, 1958.
7. Fontana, R. S., and Edwards, J. E.: Congenital cardiac disease: A review of 357 cases studied pathologically, Philadelphia, 1962, W. B. Saunders Company, p. 28.
8. Mounsey, P.: The diagnosis of persistent ostium primum, Brit. Heart J. 20:270, 1958.
9. Kjellberg, S. J., Mannheimer, E., Rhode, U., and Jonsson, B.: Diagnosis of congenital heart disease, ed. 2, Chicago, 1959, The Year Book Publishers, Inc., p. 484.
10. DuShane, J. W., Weidman, W. H., Brandenburg, R. O., and Kirklin, J. W.: Differentiation of inter-atrial communications by clinical methods. Ostium secundum, ostium primum, common atrium and total anomalous pulmonary venous connection, Circulation 21:363, 1960.
11. Braunwald, E., Boss, B. S., Morrow, A. G., and Roberts, W. C.: Differential diagnosis of mitral regurgitation in childhood. Clinical Pathological Conference at the National Institute of Health, Ann. Int. Med. 54:1223, 1961.
12. Al Omeri, M., Bishop, M., Oakley, C., Bentall, H. H., and Cleland, W. P.: The mitral valve in endocardial cushion defect, Brit. Heart J. 27:161, 1965.
13. Cooley, D. A.: Results of surgical treatment of atrial septal defects, particular consideration of low defects including ostium primum and trioventricular canal, Am. J. Cardiol. 6:605, 1960.
14. Dubost, C., and Blondeau, P.: The surgical repair of persistent trioventricular canal. Results in 26 operative cases, Am. J. Cardiol. 6:611, 1960.
15. Maloney, J. V., Marable, S. A., and Mulder, D. G.: The surgical treatment of common trioventricular canal, J. Thoracic & Cardiovas. Surg. 43:84, 1962.
16. McGoon, D. C., DuShane, J. W., and Kirklin, J. W.: The surgical treatment of endocardial cushion defects, Surgery 46:185, 1959.
17. Baron, M. G., Wolf, B. S., Steinfeld, L., and Van Mierop, L. H. S.: Endocardial cushion defects. Specific diagnosis by angiocardiography, Am. J. Cardiol. 13:162, 1964.
18. Humphries, J. O., and McKusick, V. A.: The differentiation of organic and "innocent" systolic murmurs, Prog. Cardiovas. Dis. 5:152, 1962.
19. Liebman, J., and Nadas, A. S.: The vectorcardiogram in the differential diagnosis of atrial septal defect in children, Circulation 22:956, 1960.
20. Burchell, H. B., Du Shane, J. W., and Brandenburg, R. O.: Electrocardiogram of patients with trioventricular cushion defects (defects of trioventricular canal), Am. J. Cardiol. 6:578, 1960.
21. Toscano-Barbosa, E., Brandenburg, R. O., and Burchell, H. B.: Electrocardiographic studies of cases with intracardiac malformation of the trio-ventricular canal, Proc. Staff Meet. Mayo Clin. 31:513, 1956.
22. Beregovich, J., Bleifer, S., Donoso, E., and Grishman, A.: The vectorcardiogram and electrocardiogram in persistent common trioventricular canal, Circulation 21:63, 1960.
23. Neufeld, H. N., Titus, J. L., DuShane, J. W., Burchell, H. B., and Edwards, J. E.: Isolated ventricular septal defect of the persistent common trioventricular canal type, Circulation 23:685, 1961.
24. Braunwald, E., Morrow, A. G., and Cooper, T.: Left ventricular angiocardiography in the diagnosis of persistent trioventricular canal, and related anomalies, Am. J. Cardiol. 5:802, 1959.
25. Edwards, J. E.: The problem of mitral insufficiency caused by accessory chordae tendineae in persistent common atrioventricular canal, Proc. Staff Meet. Mayo Clin. 35:299, 1960.
26. Levy, M. J., and Edwards, J. E.: Anatomy of mitral insufficiency, Prog. Cardiovas. Dis. 5:119, 1962.
27. Edwards, J. E., and Burchell, H. B.: Pathologic anatomy of mitral insufficiency, Proc. Staff Meet. Mayo Clin. 33:497, 1958.
28. Monquin, M., Brun, P., Chartrain, E., Laborgne, P., and Dagrain-Delorge, J.: L'angiocardiographie dans les canaux trioventriculaires avec fente mitrale, Arch. Mal. Coeur 52:1801, 1959.
29. Edwards, J. E., Carey, L. S., Neufeld, H. N., and Lester, R. G.: Congenital heart disease correlation of pathologic anatomy and angiocardiography, Vol. 1, Philadelphia, 1965, W. B. Saunders Company, p. 222.
30. Hancock, E. W.: Assessment of mitral valve disease by left heart catheterization, Brit. Heart J. 21:389, 1959.
31. Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: Left atrial pressure pulse in mitral valve disease, Circulation 16:399, 1957.
32. Levinson, G. E., Stein, S. W., Carleton, R. A., and Abelmann, W. H.: Measurement of mitral regurgitation in man from simultaneous atrial and arterial dilution curves after ventricular injection, Circulation 21:720, 1961.
33. Arvidsson, H.: Angiocardiographic observations in mitral valve disease, Acta Radiol. Suppl. 158, 1958.
34. Ross, R. S., and Criley, J. M.: Contrast radiography in mitral regurgitation, Prog. Cardiovas. Dis. 5:195, 1962.
35. Somerville, J.: Clinical assessment of the function of the mitral valve in atrioventricular defects related to the anatomy, Am. Heart J. 71:701, 1966.

Unusual arrhythmias after corrective surgery for transposition of the great vessels

J. R. Zuberbuhler, M.D.
S. R. Bauersfeld, M.D.
Pittsburgh, Pa.

In this hospital 5 children with complete transposition of the great vessels have been successfully operated on using the technique described by Mustard.[1] Preoperative electrocardiograms showed right axis deviation, right ventricular hypertrophy, and regular sinus rhythm. After operation the right axis deviation and right ventricular hypertrophy persisted in all. 2 of the 5 developed very unusual arrhythmias, probably as a result of surgical trauma to the sinoatrial (S-A) and/or atrioventricular (A-V) nodes.

Case presentations

Case 1.—J. T. This 5-year-old boy had been cyanotic since birth. An atrial septectomy had been performed under hypothermia when he was 1 month old, because of marked respiratory distress and intense cyanosis. When he was 5 years old cardiac catheterization and selective cineangiocardiography confirmed the diagnosis of complete transposition of the great vessels and demonstrated an atrial septal defect with bidirectional shunting. No ventricular septal defect was present. Left ventricular and pulmonary arterial pressures were low. An electrocardiogram showed right axis deviation, right ventricular hypertrophy and regular sinus rhythm (Fig. 1). Two months later the operative technique described by Mustard was carried out. (In this procedure, much of the atrial septum is removed and a pericardial patch is then inserted into the atrium in such a way as to reroute systemic venous return into the new "left" atrium, the left ventricle, and transposed pulmonary artery. The patch also directs pulmonary venous return into the new "right" atrium, right ventricle and transposed aorta. The circulatory abnormality created by the transposition is thus corrected.) In the immediate postoperative period an A-V nodal rhythm was present and no P waves were seen. Two months after operation an electrocardiogram showed an escape capture bigeminy (Fig. 2,*A*). The first beat of each pair was an A-V nodal escape beat and the second was an S-A nodal capture. The apparent S-A nodal rate was 28 per minute. It is possible that a second-degree S-A nodal block may have caused the low atrial rate. Four months after operation an intermittent A-V nodal escape rhythm was present (Fig. 2,*B*). P waves appeared intermittently at a rate of 78 per minute and were followed by QRS complexes after a 0.14-second P-R interval. At times, no P waves were present and either a third-degree S-A nodal block or an S-A nodal arrest was present. Eleven months after operation the boy was active, without symptoms, and had no cyanosis. The electrocardiogram showed sinus bradycardia at a rate of 44 per minute.

Case 2.—S.D. This 6-year-old girl had been cyanotic since birth. Increasing cyanosis, respiratory distress, and lethargy led to atrial septectomy when she was 4 months old. Marked clinical improvement occurred, but by the time she was 6 years old cyanosis had again become intense. An electrocardiogram showed severe right axis deviation, right ventricular hypertrophy, right atrial enlargement, and regular sinus rhythm (Fig. 3).

From the Department of Pediatrics, University of Pittsburgh School of Medicine, and Children's Hospital of Pittsburgh, Pittsburgh, Pa.

This study was supported in part by grants from the Beaver County Heart Association and the Association for Care of Cardiac Children, Pittsburgh, Pa.

Received for publication July 14, 1966.

Address: Children's Hospital of Pittsburgh, 125 DeSoto St., Pittsburgh, Pa., 15213.

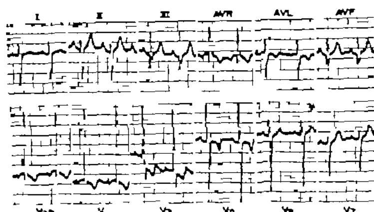


Fig. 1 Case 1. Preoperative electrocardiogram.

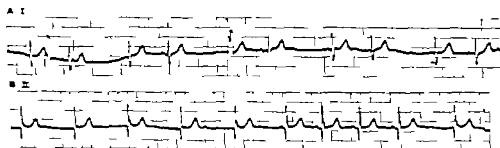


Fig. 2 Case 1. A. Lead I. Escape capture bigeminy with very slow atrial rate. B. Lead II. Intermittent S-A nodal arrest or third-degree block with A-V nodal escape rhythm.

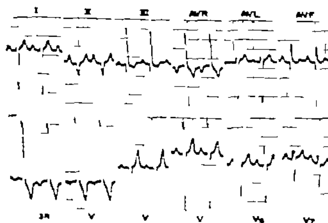


Fig. 3. Case 2. Preoperative electrocardiogram.

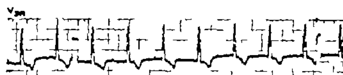


Fig. 4. Case 2. Third-degree A-V block with A-V nodal rhythm.

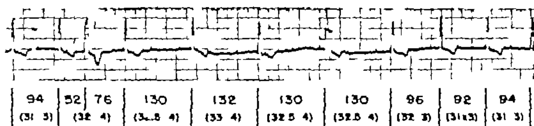


Fig. 5. Case 2. Third-degree A-V block. Variable ventricular rate probably due to second level of block within the A-V node. Intervals are in hundredths of a second.

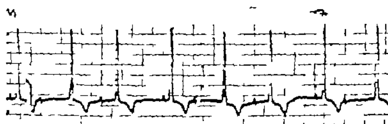


Fig. 6. Case 2. Second-degree A-V block with A-V nodal escape rhythm.

Cardiac catheterization and selective cineangiocardiography confirmed the presence of complete transposition of the great vessels and showed bidirectional shunting at the atrial level. No ventricular septal defect was present; left ventricular pressures were consistently lower than right ventricular pressures. Correction by the Mustard technique was carried out. A tracing recorded on the sixth postoperative day (Fig. 4) showed third-degree A-V block with an A-V nodal focus controlling the ventricles. This tracing could represent an A-V nodal tachycardia at a rate of 176 with a 2:1 block within the A-V node. Another tracing obtained 3 weeks after operation again showed third-degree A-V block, but the ventricular rhythm was irregular (Fig. 5). The R-R intervals clustered about 0.94 second and 1.30 seconds. The least common denominator is approximately 0.32 second, suggesting an A-V nodal tachycardia at a rate of 188 per minute, with variable 3:1 and 4:1 block within the A-V node itself. The third QRS is wide and follows an interval of 0.52 second. It probably represents a premature ventricular contraction, but could represent an A-V nodal beat with first-degree intranodal block and aberrant conduction. An alternative explanation would involve postulating a marked A-V nodal arrhythmia with aberrant conduction of the beat with the shortest P-R interval. This degree of A-V nodal arrhythmia would be most unusual, and this explanation seems to be less likely. Six months after operation the child was clinically well, and the electrocardiogram shown in Fig. 6 was obtained. The third and sixth QRS complexes follow a P-R interval of 0.20 second, occur early, and represent conducted S-A nodal beats. P waves are buried in the T waves of beats 3 and 6 and are presumably buried in beats 2, 5, and 8. P waves immediately follow the T waves in the first, fourth, and seventh beats but are not conducted. A second-degree A-V block thus appears to be present. The tracing could also be interpreted as an A-V dissociation in which a nodal pacemaker becomes dominant in spite of a faster sinus mechanism because of prolonged refractoriness (following beats 1, 4, and 7).

Discussion

The arrhythmias noted in two of the five instances of successful corrective procedures done in this institution for transposition of the great vessels were

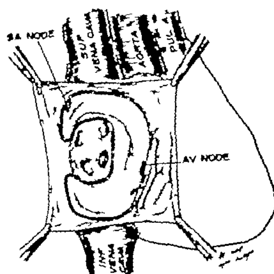


Fig. 7. Sketch showing proximity of S-A and A-V nodes to the suture line in the Mustard procedure.

quite unusual. In the first description of this type of procedure, Mustard mentioned only a few ectopic beats, and in a second paper he mentioned no arrhythmias. Aberdeen and associates, however, described 9 operated cases, 7 of which were successful. Of these 5 patients had supraventricular arrhythmias in the first weeks after operation. Three of these patients were discharged in atrial flutter with 2:1 A-V block.

The surgical procedure described by Mustard[1] involves the insertion of a pericardial patch into the atria. The suture line of the patch runs very close to the S-A and A-V node (Fig. 7). The arrhythmias in Case 1 consisted of variable second and third-degree S-A nodal block, which could have resulted from trauma to the S-A node. The resultant slow atrial rate led to A-V nodal escape beats and to an escape capture bigeminy. Schamroth recently described such an arrhythmia, commenting on its extreme rarity and citing two other examples from the literature. In Case 2 there appeared to be two levels of A-V nodal block. The upper level resulted in third-degree A-V block and A-V dissociation. An A-V nodal tachycardia at a rate of 188 per minute was present, but a slower ventricular rate indicated a second-degree block between the A-V nodal pacemaker and the ventricles. Both levels of block may have resulted from surgical trauma to the region of the A-V node. Katz has described a similar arrhythmia with two levels of A-V block.[7] Subsequent tracings have shown a lesser degree of A-V nodal block. In neither case was digitalis a factor in the arrhythmias.

Both children have had excellent results from their operation and although arrhythmias persist they do not at present appear to be a threat to life. An effort to avoid the region of the S-A node and A-V node in placing the pericardial patch seems to be advisable and a modification originated by Aberdeen utilizes part of the original interatrial septum in the placing of the pericardial patch avoiding the regions of the S-A and A-V nodes.

Summary

Two of five successful corrective surgical procedures for transposition of the great vessels have resulted in unusual arrhythmias. One consisted of a variable degree of S-A nodal block and the other of two levels of block in the A-V node. Both probably resulted from surgical trauma.

REFERENCES

1. Mustard, W. T.: Successful two-stage correction of transposition of the great vessels, Surgery 55:469, 1964.
2. Mustard, W. T., Keith, J. D., Trusler, G. A., Fowler, R., and Kidd, L.: The surgical management of transposition of the great vessels, J. Thoracic & Cardiovas. Surg. 48:953, 1964.
3. Aberdeen, E., Waterston, D. J., Carr, I., Graham, G., Bonham-Carter, R. E., and Subramanian, S.: Successful correction of transposed great arteries by Mustard's operation, Lancet 1:1233, 1965.
4. Schamroth, L., and Dubb, A.: Escape capture bigeminy. Mechanisms in S-A block, A-V block, and reversed reciprocal rhythm, Brit. Heart J. 27:667, 1965.
5. Bradley, S. M., and Marriott, H. J. L.: Escape capture bigeminy. Report of a case of A-V dissociation initiated by 2:1 S-A block with resulting bigeminal rhythm, Am. J. Cardiol. 1:640, 1958.
6. Padilla, T., and Cossio, P.: Disociación auriculoventricular por interferencia, con captura ventricular. La parasistolia ni evidente, Semana Méd. (Buenos Aires) 37:1412, 1930.
7. Katz, L. N., and Pick, A.: Clinical electrocardiography. The arrhythmias, Philadelphia, 1956, Lea & Febiger, p. 651.
8. Aberdeen, E.: Personal communication from D. J. Waterston, The Hospital for Sick Children, Great Ormond Street, London, England.

Experimental and laboratory reports

Methods and physical characteristics of the kinetocardiographic and apexcardiographic systems for recording low frequency precordial motion

William H Bancroft Jr M S
*E E Eddleman Jr M.D***
Birmingham Ala

Since more emphasis is being placed on the use of kinetocardiography and apexcardiography as possible diagnostic aids,[1-4] a careful determination of the physical characteristics of the two systems which are most frequently employed appears to be useful The following study involves a strictly mechanical determination of the physical characteristics of the given units, using a vibration table as the displacement source for measuring frequency and phase angle response

Methods

A specialized vibration table was developed to produce accurately calibrated displacements varying in amplitude from 002 to 05 inch Frequencies could be varied from 0 to 100 cycles per second The table consists of a lever coupled to an eccentric shaft. All moving parts have precision ball bearings and shafts. A variable speed motor drives the eccentric shaft and is coupled to the shaft with neoprene belts. The frequency is determined by an electronic counter accurate to ± 0 1 cycle per second Amplitude of the displacements was determined by a measuring microscope accurate to ± 0001 inch

A photoelectric displacement transducer† was first tested on the table and found to be linear over the full range of frequencies tested within the limits of accuracy of the measuring devices used The output of the photoelectric transducer was recorded using the D C. channels of an oscilloscopic recorder.‡ Amplitudes of output were measured with an accuracy to two significant figures at frequencies varying from 2 to 50 cycles per second The amplitudes did not vary using this number of significant figures. Hereafter the photoelectric transducer was used as a standard for measurements of displacement.

The kinetocardiographic pickup includes a three section bellows‖ connected to a pressure transducer‖ by a 20-cm length of

With the technical assistance of Larry K. Larkin, Electronics Technician, Veterans Administration Hospital
From the Medical Service Veterans Administration Hospital, and Department of Medicine, Medical College of Alabama, Birmingham, Ala.
Aided by United States Public Health Service Grants No. HE 0-3080, HE 0 4151, and HE 0-9423
Received for publication July 8 1966
*Physicist, Medical Research, Veterans Administration Hospital; Instructor in Physics, Medical College of Alabama.
**Associate Chief of Staff for Research, Veterans Administration Hospital; Professor of Medicine Medical College of Alabama.
†Schwarzer Instrument Company Framingham, Mass.
‡Electronics for Medicine DR-8.
‖Made by Kelvin & Hughes America Corporation Annapolis, Md.
‖Statham PS-A.

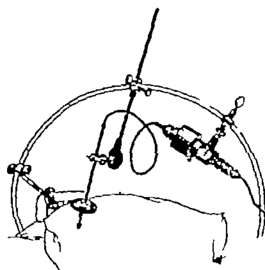


Fig. 1. Diagram of the kinetocardiographic setup used in recording low-frequency movements. The bellows in the center of the photograph is connected by Tygon tubing t the P5A Statham transducer mounted on the crossbar. Thus, the probe on the other end of the bellow ca be placed perpendicular to any point on the chest all to record movements t that position. Show is the two-flange bellows which is perfectly satisfactory however at the present time this laboratory is using the three flange unit.

¼-inch Tygon tubing (Fig. 1).[4] The bellows has a spring constant of 80 pounds per inch with a natural frequency of 220 cycles per second. The bellows is mounted from a fixed point above the chest wall (iron crossbar) which allows the recording of absolute displacement movements of the chest wall at any point desired. The average force applied to the chest wall is 2 pounds, however this pressure and rigidity of the bellows apparently does not in itself alter the movements of the chest wall since identical traces can be obtained with the photocell. This will be discussed subsequently. The probe is applied usually in the intercostal spaces. This is done because there is less discomfort to the patient than recording directly on the ribs, although records from adjacent positions are almost identical in contour. Amplitude response of the system was measured as that described for the photocell. Phase shift was determined by comparing the simultaneously recorded outputs of the kinetocardiogram and photoelectric transducers. At higher frequencies accuracy of this measurement was ±10 degrees.

Linearity of the system was tested by measuring the amplitude response at varying displacements. To determine the effect of length of tubing and type of tubing the amplitude response was determined using several different lengths of Tygon tubing gum rubber and neoprene tubing.

The apexcardiographic pickup is a funnel type pressure pickup connected by a ⅛-inch I.D. ⅛-inch wall thickness gum rubber tubing to a piezoelectric microphone. The funnel is 2 inches in diameter 1 inch to the closed apex with the outlet to the microphone situated approximately ¼ inch above the open end of the bell. The outlet tube is ⅛ inch in diameter. Clinically the funnel is mounted upon the chest wall so that relative motions between the central portion and the rim are recorded. This is the standard apparatus and procedure for recording the apexcardiogram.

Since the apexcardiographic pickup measures the change in pressure of the air in the final microphone chamber as a result of differential motion the response characteristics of this system are more difficult to obtain. To approximate the chest and to generate differential motion a double sheet of .01 inch elastic rubber was stretched across the end of a plastic funnel. The volume of the funnel was approximately 300 c.c. The pressure in the system could be changed in a sine wave fashion by connecting the funnel to a bellows mounted on the vibration table. The amplitude and phase shift response of the membrane was determined by placing the photoelectric transducer on the center of the rubber diaphragm and ascertaining its characteristics. The apexcardiographic transducer was then centered on the diaphragm and measurements were made. The pressure in the system was monitored by a Statham strain-gauge transducer (P23D). A correction factor for the frequency variation of the diaphragm was made by dividing the displacement amplitude of the diaphragm determined by the photocell output at 1 cycle per second by its amplitude over the range of frequencies studied. The corrected or true response the apexcardiographic transducer is

the product of the correction factor and the amplitude of the transducer output at each frequency This procedure corrects for the variation in the frequency response of the diaphragm in order to ascertain only the frequency characteristics of the apexc rdiograph The phase shift correction was performed *by a direct algebraic ad* dition of the phase shift of the diaphragm and phase shift of the apexcardiographic transducer The system in no way approxi mates the chest wall characteristics but offers a means by which the apexcardiographic transducer funnel and tubing can be tested as a unit and not just the piezoelectric transducer

To study the possibility of variation in technique as used clinically as well as inherent instrumentation error kinetocardiograms and apexcardiograms were taken sequentially in 2 normal subjects on 9 different days The kinetocardiograms were recorded by a technician whereas the apexcardiograms were taken with care by a physician

Results

Frequency response (*Figs 2 and 3*) The kinetocardiographic system has an obvious resonance at 80 cycles per second (Fig 2) This system displays a smooth response curve ±2 db from D C to 28 cycles per second The apexcardiographic system (Fig 3) is ± 1 db from 0 1 to 20 cycles per second with a rapid rise above 22 cycles per second and a resonance at 25 as well as somewhere above 80 cycles per second The response curve has another small resonance peak at 15 cycles per second causing deviations from a smooth curve.

Phase shift (*Figs 2 and 3*) The kinetocardiographic system showed a surprising lack of phase shift Within the limits of accuracy of the measuring procedure the kinetocardiogram showed zero phase shift in the range 2 to 40 cycles per second The apexcardiographic system ranges from 65 degrees lead at cycles per second as well as a 138 degrees lead at 22 cycles per second

Linearity Fig 4 shows the linearity of the kinetocardiographic system at 1 cycle per second using a 40-cm. Tygon tube connecting the bellows and transducer The ordinate is the output, in millivolts of the pressure transducer The abscissa is the displacement of the vibration table producing the output The output is linear

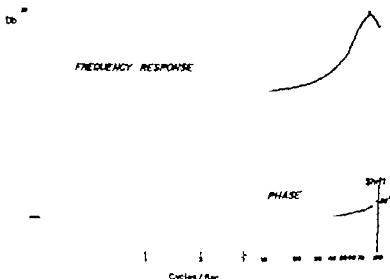


Fig 2. The frequency response t phase characteristics of the kinetocardiographic system measured in decibles and degrees. Note that the kinetocardiographic system is linea within 2 decibels to about 20 cy les per second However there is slow gradual rise reaching resonance at approximately 80 cycles per second N phase shift occurs until 30 cy les per second. One peculiar aspect of this system is the fact that the shift in phase is not 90 degrees at point of resonance however it should be noted that this is not a simple electrical system, but a complex system involving both electrical h nd mechanical transmission, and that therefore, the 90-degree phase shift at point of resonance does not necessarily occur

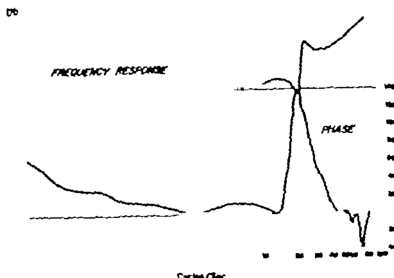


Fig. 3 The frequency response and phase characteristics of the apexcardiographic system as determined by the apparatus described. The cycles per second are given in the lower portion of the figure. Note that the apexcardiogram is essentially linear in response from one-tenth cycle per second to approximately 20; however, there is a sharp rise in frequency response at approximately 20 cycles per second. The main resonance peak was apparently about 30 cycles per second. The phase characteristics are considerably abnormal and are distorted both in the lower frequency range and in the upper frequency range. There is approximately 60 degrees of phase shift at one-tenth cycle per second and more than 130 degrees of phase shift at approximately 20 cycles per second. This indicates that the use of the apexcardiographic system is not reliable in terms of phase characteristics.

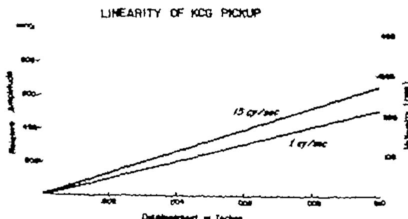


Fig. 4 The response of the kinetocardiographic pickup over various changes in amplitude. Note that the kinetocardiographic apparatus is linear both at 1 and 15 cycles per second.

at all frequencies. It was found to be impractical to test the linearity of the apexcardiographic system with the apparatus as described.

Effect of tubing on response. Fig. 5 displays the change in frequency response of the kinetocardiographic systems with a change in the length of the tubing connecting the bellows and transducer. The shorter the tubing and the more rigid the tubing the better is the frequency response.

Discussion

The kinetocardiographic apparatus used in recording precordial displacement movements involves the suspension of a linear

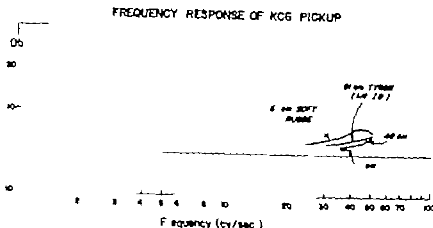


Fig 5 The frequency response curv for the kinetocardiographic system using various lengths and types of tubing t connect the bellow to the Statham PSA transducer Not that the best response is obtained with the shortest Tygon t bing (rree labeled 9 cm).

displacement device from a fixed point above the chest wall Because of the position of the mount these movements represent absolute displacement movements of the precordium This technique does not record tangential chest wall motion but only those movements perpendicular to the chest wall The name kinetocardiography has been applied rather than apex cardiography which refers to recording the relative movements of the apex with the pickup mounted on the chest wall In addition with the kinetocardiographic technique recordings can be made at many positions over the anterior chest wall not just at the apex Thus it has been believed that a separate term kinetocardiography is justified Since the photocell pickup was linear over a wide range of frequencies in the present study it is obvious that it is the more ideal transducer for sensing low frequency precordial movements than is either the bellows or the apexcardiographic transducer However because of the limitations in the travel of the probe (¾-inch is the one used) it becomes a most difficult pickup to position clinically Thus the bellows has continued to be used in this laboratory since its frequency response is adequate for the types of motion being recorded. It is easily applied by a technician and the records are reproducible from day to day without a physician being involved in the procedure. Although the bellows system has a resonance at 80 cycles per second this is sufficiently high with respect to the frequencies which are being recorded not to add a significant distortion to the records, and is essentially free from phase shift. In addition the records obtained with the photocell and bellows are almost identical (Fig 6) *The rigidity of the bellows and pressure applied to the chest wall does not alter the movements since the photocell records kinetocardiograms which are identical when taken from the same point on the precordium*

The apexcardiogram on the other hand does not have a smooth linear response curve although the response from 1 to 0 cycles per second appears to be satisfactory (Fig 3) Even more important is the phase shift encountered which is appreciable at certain frequencies and could distort physiologic time relationships. A recent study indicates that the physiologic time relationships of the apexcardiogram are distorted The phase shifts encountered possibly account for these findings.

Reproducibility of the two techniques is not a part of this study However it should be mentioned that the kinetocardiographic traces are highly reproducible from day to day in the same subject even when taken by a technician. Fig 7 presents 4 out of 9 kinetocardiograms taken on consecutive days. On the other hand reproducibility of the apexcardiogram depends upon the skill of the physician taking

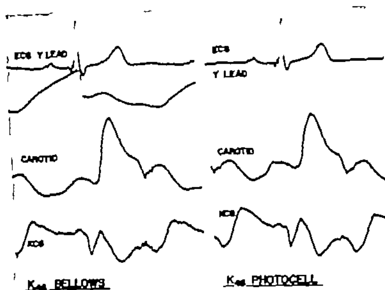


Fig. 6. Kinetocardiographic records obtained with the two types of transducers: *left,* with the bellows transducer as described; *right,* with a photoelectric cell in which the spring constant is considerably less than that with the bellows. In addition, the photocell record, as pointed out, has a linear frequency response over the ranges tested (0-80 cycles per second). Note that the traces are essentially identical, indicating that the kinetocardiographic records as obtained with the bellows system faithfully reproduce the movements of the chest wall, and that the rise in frequency response of the kinetocardiographic apparatus in the high-frequency range insignificantly affects the contour of the kinetocardiographic records. (From Eddleman, E. E., Jr., and Harrison, T. R.: The Kinetocardiogram in Patients with Ischemic Heart Disease, Progress in Cardiovascular Diseases 6(3): 189-211, November, 1963, by permission of the publisher.)

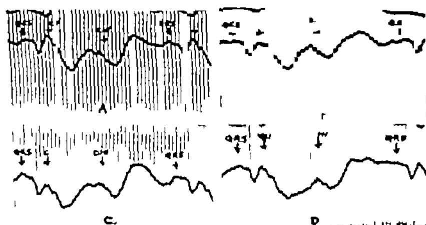


Fig. 7. Four of ten kinetocardiographic curves obtained from a normal individual. These curves were recorded by a technician at daily intervals from the region of the apex of the heart. The most extreme variations on the curves were selected for presentation. *QRS,* The onset of the QRS complex. *CU,* The onset of the carotid upstroke. *CIN,* The end of ejection as determined from the carotid incisural notch. Note that there is some variation from day to day; however, the main contours of the curves are identical.

Fig. 8. A-D. Four extreme variations in the apexcardiogram from the same individual. The sensitivity of the apparatus was maintained constant and records were obtained over a 10-day period. In contrast to the kinetocardiogram, a physician recorded these in an attempt to obtain similar record from day to day. *QRS*: The onset of the QRS complex. *CL*: The onset of ejection determined from the carotid upstroke. *CIN*: The end of ejection as determined from the carotid incisural notch. Note that there is considerable variation in the part just before the QRS as well as in the midsystolic and filling portions of the curves. *D* does represent an extreme variation and is considerably different from the other records. It is obvious that this would not be considered to be a suitable apexcardiogram; however, it does point out the marked variation that can occur by slightly different positioning of the transducer from day to day.

the record. Nevertheless, Fig. 8 does present some of the variations encountered when a physician records consecutive daily records on a normal subject. The examples are extreme and the trace in Fig. 8 *D* would not be accepted as a usable record, but the figure does illustrate possible variations which are minimal with the kinetocardiographic technique.

There are other important aspects in recording low frequency displacement movements besides the type of transducer. The type of mount of the transducer is particularly significant. The apexcardiographic transducer is mounted on the chest wall and records only differential motion between the enclosed portion of the chest and the rim. This can result in records which may be difficult to interpret. For example, if the rim moves outward and there is a comparable movement of the apex (or the central portion within the rim), no movement will be recorded, since no relative motion between the center and the rim has occurred. Fig. 9 illustrates several theoretical situations which might occur. A defect may exist in any system which is mounted on the chest wall. On the other hand, a kinetocardiograph is mounted from a fixed point above the patient so that only absolute movements of the point on the chest wall where the probe is placed is sensed. In addition, it should be pointed out that *kinetocardiographic curves more closely resemble the movements detected by palpation at the bedside*, since the physician is feeling the chest wall from a fixed point above the patient. The position of the patient during the recording procedure offers another facet of the problem. The apexcardiograms are recorded with the patient turned obliquely on the left side. It is difficult to achieve the proper position in different patients as well as in the same patient from day to day. This may account for some variations noted in Fig. 8. On the other hand, the kinetocardiographic system used the recumbent position which eliminates this difficulty.

Apexcardiography offers an additional

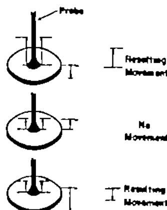


Fig. 9. A theoretical consideration of the problems encountered with the apexcardiographic system. The diagram represents three possible theoretical situations which might occur to make the movements of the chest wall difficult to interpret with the apexcardiographic technique. The probe represents the movable central portion of the chest wall within the rim of the funnel. In the top diagram, the center portion within the funnel may move a considerable degree outward (upward), whereas, if the funnel portion which rests upon the chest wall moves inward, the resultant motion is altered in amplitude response. In the center diagram, if both the probe and the rim move the same degree no response will be recorded. In the lower figure, if the rim moves more in the opposite direction than does the central portion, a paradoxical response will occur. (From Eddleman, E. E., Jr., and Harrison, T. R., The Kinetocardiogram in Patients with Ischemic Heart Disease, Progress in Cardiovascular Diseases 6(3):189-211, November 1963, by permission of the publisher.)

problem in technique and that is the positioning of the funnel. It usually requires a physician and repeated exploration of the apical area before a suitable impulse is obtained. This can be seen in Fig. 8,D, in which slight differences in positioning result in marked changes in the contour. This too may be a factor which influences the reproducibility, although this should be minimized with the increasing skill of the physician. However, the record finally decided upon is *highly arbitrary* and varies considerably in contour and amplitude with slight shifts in position and pressure. The size of the funnel also affects the apexcardiogram and is not standardized from one laboratory to another. Fig. 10 illustrates the variation in contour obtained by varying the size of the funnel. The apexcardiographic technique is limited in still another facet. Only records of the apex impulse can be made with any regularity. Thus, records from the other areas of the precordium which may provide a great deal of clinical information are often omitted.[15] For example, right ventricular abnormalities are best detected in the parasternal areas and bulges due to myocardial infarctions in the V and V positions.[13,1] There is little doubt that the physical system of the kinetocardiographic technique appears to be superior to that of the apexcardiographic. This is not to dispute the fact that the apexcardiogram may clinically be of value. It should be mentioned that the bellows is not critical in the accurate recording of displacement precordial movements in that any reasonable linear displacement transducer mounted from a

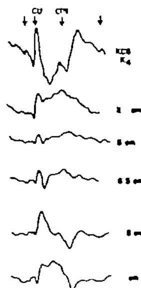


Fig. 10. The changes in the contour of the apexcardiogram which can occur as a result of variations in the diameter of the funnel used for recording the traces. The top record is a kinetocardiographic trace for comparison. Q, Onset of the QRS complex. CI, Onset of ejection as determined from the carotid upstroke. CIV, End of ejection as determined from the carotid incisural notch. Note that as the size of the funnel is changed from 2.5 cm. to 11 cm. in diameter, marked variation in the contour of the records occurs. This points out the necessity of using a funnel of standard-size diameter in recording the apexcardiographic records.

fixed point above the chest wall yields records identical to those described

Summary

1 The physical systems of the kinetocardiographic and apexcardiographic techniques are presented

2 The kinetocardiographic system is linear in the low frequency ranges D C 20 cycles per second however there is a resonance at 80 cycles per second The apexcardiographic system is linear from 1 to 20 cycles per second however the rise in response in the upper frequency range is distorted by several resonances.

3 No significant phase shift occurs in the kinetocardiographic system but the apexcardiographic system has considerable phase shift from 1 to 2 cycles per second and in the higher frequency ranges.

4 A discussion of the comparison between the two systems is presented

We wish to express our appreciation to Mr Harry Germaglan Medical Illustration Division Veterans Administration Hospital Birmingham Ala for preparation of the illustrations

REFERENCES

1 Eddleman E E Jr Holt J H and Bancroft W H Jr Computer analysis of the kinetocardiogram from patients with atrial septal defects, Am Heart J 71:435 1966
2 Schweizer W Bertrab, R V and Reust, Ph. Kinetocardiography in coronary artery disease, Brit Heart J 27:263 1963
3 Beilin, L and Mounsey P The left ventricular impulse in hypertensive heart disease Brit Heart J 24:409 1962
4 Benchimol, A and Dimond, E. G. The apex cardiogram in normal older subjects and in patients with arteriosclerotic heart disease Effect of exercise on the A wave Am. Heart J 65 789 1963
5 Eddleman E. E Jr Willis, K., Reeves, T J and Harrison T R: The kinetocardiogram I Method of recording precordial movements, Circulation 8:269 1953
6. Eddleman E. E., Jr Cardiovascular dynamics—Technics for indirect measurements. Clinical cardiopulmonary physiology New York 1960, Grune & Stratton Inc., p. 158.
7 Eddleman, E. E Jr : The kinetocardiogram—Ultra low-frequency precordial movements, I Cardiology: An encyclopedia of the cardiovascular system, Vol. 2, Chapter 3 pp. 63 (Supp.)–70X (Supp.) New York 1962, McGraw Hill Book Company Inc.
8. Benchimol, A. and Dimond, E. G The normal and abnormal apexcardiogram—Its physiologic variation and its relation to intracardiac events, Am. J Cardiol. 12 368, 1963
9 Tavel, M E Campbell, R. W Feigenbaum, H and Steinmetz, E. F The apex cardiogram and its relationship to haemodynamic events within the left heart Brit. Heart J 27:829 1965.
10. Eddleman F E Jr Kinetocardiographic changes in ischemic heart disease Circulation 31:650 1965.
11 Tucker W T Knowles, J L. and Eddleman, F E., Jr Mitral insufficiency: Cardiac mechanics as studied with the kinetocardiogram and ballistocardiogram, Circulation 12:278, 1955.
12. Eddleman E. E., Jr Yoe R H Tucker W T Knowles, J L., and Willis, K. The dynamics of ventricular contraction and relaxation in patients with mitral stenosis as studied by the kinetocardiogram and ballistocardiogram, Circulation 11 774 1955
13. Davie J C Langley J O Dodson, W H and Eddleman F E., Jr Clinical and kinetocardiographic studies of paradoxical precordial motion, Am. Heart J 63 775 1962.
14 Soh, S. K., and Eddleman, E. E., Jr : Kinetocardiographic findings of myocardial infarction, Circulation 19:531 1959

Observations on sustained pulsus alternans during hypothermia

Walter L. Floyd, M.D.
Marcus L. Dillon, M.D. **
Durham, N. C.

The phenomenon of alternation of peripheral pulse pressure has been of interest to clinicians and investigators since its original description by Traube in 1872. Despite numerous clinical and laboratory observations which have postulated a variety of "myogenic"[2,4] and "hemodynamic"[3] factors in the genesis of pulsus alternans, the underlying mechanisms of ventricular alternation have never been defined. While involved in a study of altered ventricular pressure and ejection dynamics during hypothermia, we noted the spontaneous occurrence of pulsus alternans during the period of reduced myocardial temperature. We then noted that we could induce and maintain pulsus alternans for prolonged periods, which allowed detailed observations on the pressure and ejection dynamics of the left ventricle during peripheral alternans. It is thought that these observations define some of the mechanisms involved in the initiation and perpetuation of ventricular alternation, and that an understanding of the dynamics under the conditions studied will aid in future clarification of its occurrence in man.

The purpose of this communication is (1) to illustrate the occurrence of pulsus alternans during hypothermia, (2) to discuss the probable relationship of ventricular alternation to the abnormality in myocardial contraction and relaxation produced by hypothermia, and (3) to demonstrate the modification of pulsus alternans by other factors, including heart rate, atrial filling pressure, and ventricular outflow resistance.

Materials and methods

Observations were made on 2[illegible] mongrel dogs anesthetized with chloralose and urethane and maintained on positive pressure breathing. The heart was exposed by a sternum-splitting incision, and the ascending aorta, left atrium, and left ventricular cavity were cannulated via the right carotid artery, left atrial appendage, and cardiac apex, respectively. Continuous measurement of phasic aortic, left atrial, and left ventricular pressures were made using Statham strain gauges. Phasic aortic flow was determined by a square-wave electromagnetic flowmeter as described by Spencer and Denison. Flowmeter

From the Departments of Surgery and Medicine, Duke University School of Medicine, and the Veterans Administration Hospital, Durham, N. C.

Supported by Research Grants HE-04907, HE-08640-03, and Training Grant HTS-5360 from the National Heart Institute, United States Public Health Service.
Received for publication July 1, 1966.

*Assistant Professor of Medicine, Duke University School of Medicine; Assistant Director, Cardiovascular Disease Service, Duke University Medical Center, Durham, N. C.
**Associate Professor of Surgery and Chief of Thoracic Surgery, Veterans Administration Hospital, Durham, N. C.

probes were applied to the proximal aorta approximately 2 cm above the sinuses of Valsalva. The probes were calibrated by a previously described method after the termination of each experiment. The electrocardiogram and phasic pressure and flow curves were recorded simultaneously on a Honeywell Visicorder or Electronics for Medicine recorder at paper speeds of 100 mm per second. Heart temperature was measured by a needle thermistor inserted into the apex of the left ventricle.

In 14 animals hypothermia to minimum heart temperatures of 20 to 25° C. was induced by means of an extracorporeal method of veno-venous cooling. Blood was removed by gravity outflow from the inferior vena cava, passed through a heat exchanger and returned to the animal by pumping into the superior vena cava. Left atrial pressure was maintained constant during the cooling and rewarming period by adding or withdrawing blood from a reservoir in the extracorporeal circuit. Left atrial pressure was monitored by a water manometer attached to the left atrial cannula. Four dogs were cooled by a similar extracorporeal method except that blood removed from the inferior vena cava was returned to the animal via the femoral artery after passage through the heat exchanger. Another 4 dogs were cooled by external ice packing.

Mean aortic pressure (MAP) and *mean left atrial pressure* (MLAP) were determined by planimetry of respective pressure curves. *Stroke volume* (SV) was measured by planimetry of the portion of the flow curve above the zero flow line on five successive flow curves and by calculation of the average of these values. *Cardiac output* (CO) was measured by multiplying *heart rate* (HR) per minute and stroke volume in milliliters. The *duration of systole* (DS) was measured as beginning with the initial rise in pressure in the ventricle and extending to the point of cessation of forward flow in the aorta. This latter point corresponded to the point at which the descending limb of the flow curve crossed the zero flow line. Thus, systole included the period of isometric contraction and the duration of ejection. *Isometric relaxation* (IR) was measured as extending from the point of cessation of forward flow in the aorta to the point of equalization of ventricular and atrial pressures at which opening of the mitral valve occurred.

Complete ventricular alternans is defined as occurring when the alternate small ventricular beat is not of sufficient magnitude to open the aortic valve and produce a deflection on the aortic pressure tracing. Incomplete alternans is said to exist when the alternate small rise in ventricular pressure is of sufficient magnitude to exceed end-diastolic aortic pressure and produce an aortic pressure deflection which is smaller than the preceding beat.

By necessity the electrocardiogram and the pressure and flow tracings were recorded on the same area of recording paper. For clarity of presentation the electrocardiogram and the flow and pressure curves have been separated by tracing from the original recordings.

Observations

Of 14 animals cooled by the veno-venous method 5 developed ventricular fibrillation during the cooling or rewarming period without the appearance of pulsus alternans. Pulsus alternans lasting 15 to 45 minutes occurred in the other 9 animals during the rewarming period. Of the 4 animals cooled by venous-to-arterial pumping 2 developed pulsus alternans during the cooling period and ventricular fibrillation terminated the experiments in the other 2 animals without the appearance of alternans. Two of 4 animals cooled externally developed pulsus alternans during the cooling period. Ventricular fibrillation developed shortly after the appearance of pulsus alternans in one animal but the second animal demonstrated sustained alternans for approximately 20 minutes, and alternation disappeared spontaneously before ventricular fibrillation occurred. The following observations are confined to those animals in which pulsus alternans was successfully induced.

I. Relationship of altered myocardial contraction, abnormal myocardial relaxation, and heart rate to the occurrence of pulsus alternans under hypothermia. The induction of hypothermia resulted in a slowing of the heart rate, a fall in cardiac output, a decline in mean arterial pressure and prolongation of systole and isometric

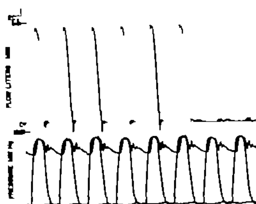


Fig 1A Occurrence of pulsus alternans during induced tachycardia nder hypothermia. ECG and flow nd pressure tracings t heart temperature of 37.2°C. HR, 158 per minute MAP 125 mm. Hg MLAP 8 0 mm. Hg SV 8 8 mL CO 1,390 mL per minute. DS 0.22 sec IR, 0 05 sec. (Time marker 0.2 sec)

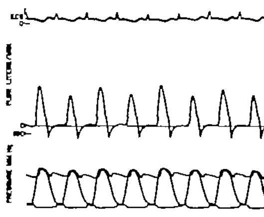


Fig 1C. Occurrence of pulsus alternans d ring induced tachycardia nder hypothermia. Tracing made 6 minutes after selecth rewarming began. Left ventricular temperature, 7.5°C HR, 150 per minut MAP 80.5 mm Hg MLAP 8 0 mm. Hg SV (mean), 2.3 mL CO 345 mL per minute. DS 0.22 sec IR, 0.13 sec Note pulsus alternans on flow nd pressure tracing



Fig 1B Occurrence of pulsus alternans during induced tachycardia nder hypothermia Observations made 1 hour after Fig 1A after cooling the heart to temperature of 23.8°C HR 60 per minute MAP 97.3 mm Hg MLAP 8 0 mm. Hg SV 10 3 mL CO 613 mL per minute DS, 0 44 sec IR, 0.34 sec Note progressive decline i rate of isometric relaxation and extension of gradual entricular relaxation i to diastolic filling period (Time marker 0.2 sec)

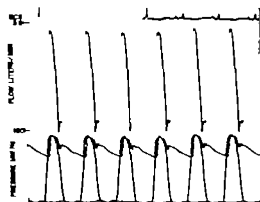


Fig 1D Occurrence of pulsu al ernans d ring doced tachycardia nder h pothermia Observations made 30 m nutes af er racing of Fig 1C Left entricle has been rewarmed 37°C HR 143 per minu MAP 1 7 mm Hg MLAP 8 0 mm. Hg SV 9 1 ml CO 1,303 ml per minute DS 0 21 sec IR 0 05 sec

relaxation in all animals. The electrocardiogram flow curves, pressure tracings, and hemodynamic data of a representative experiment in which an an mal was cooled by the veno-venous method are illustrated in Fig 1 In Fig 1A when heart temperature was 37 2°C the heart rate was 158 per m nute mean aortic pressure was 125 mm. Hg mean left atrial pressure was 8 0 mm Hg troke volume was 8 0 ml and cardiac output was 1,390 ml per minute The duration of systole was 0..2

second and the high velocity of ejection was reflected in the rapid initial rise in the intraventricular pressure and aortic flow curves. The symmetry of the aortic flow curve indicates that the ejection volume was relatively equally divided between the first and second halves of the ejection period. Isometric relaxation was brief (0.05 second) and even though the diastolic filling period was short, minimum intraventricular pressure was attained within the first half of the diastolic filling period.

After 1 hour of cooling the heart temperature fell to 23.8°C. In spite of a slowing of the heart rate to 60 beats per minute, the maintenance of a constant left atrial pressure, and prolongation of the diastolic filling period, the stroke volume rose only slightly, to 10.3 ml. Cardiac output and mean aortic pressure declined dramatically (613 ml. per minute and 97.3 mm. Hg, respectively). Duration of systole was double the normothermic value (0.44 second). The initial velocity of ejection remained rapid but the volumes of ejection in the two halves of the ejection period became disproportionate in that the major part of the volume was expelled in the first half of the ejection period and the later stages of ejection were spent with markedly reduced volume and velocity of forward flow of blood.

As compared to the twofold increase in duration of systole, an even more remarkable prolongation in the duration of isometric relaxation from 0.05 to 0.34 second occurred. It was likewise apparent that as isometric relaxation progressed, the rate of decline in pressure fell and gradual relaxation extended into the diastolic filling period. The normal early diastolic dip in intraventricular pressure was obliterated and intraventricular and intra-atrial pressure were higher early in the diastolic filling period, whereas in the normothermic animal the highest pressures occurred late in diastole.

In the 9 animals cooled by the extracorporeal venous method in which alternation occurred, pulsus alternans appeared during the initial rewarming period when an increase in heart rate was induced by selective rewarming of the region of the sinoatrial node. In the illustrated experiment the heat exchanger was reversed when the heart temperature reached 23.8°C. and blood at a temperature of 38°C. was allowed to flow into the superior vena cava. This maneuver resulted in a rapid preferential rewarming of the right heart, and rewarming of the left ventricle occurred only after a perfusion period of 30 minutes. Fig. 1C illustrates the observations made 6 minutes after rewarming was begun. The appearance of warm blood in the right heart was associated with a rapid rise in pulse rate to 150 per minute, and only minimal rewarming of the left ventricle to 27.5°C. occurred during the same period. Simultaneously, stroke volume fell to 2.3 ml. (mean) and, in spite of elevation of heart rate to precooled levels, there was a further reduction in cardiac output to 345 ml. per minute. Aortic pressure fell to 80.5 mm. Hg, duration of systole fell to 0.2 second, isometric relaxation remained slow (0.13 second), and the diastolic filling period was abbreviated.

The impressive alteration of the character of intraventricular and intra-atrial pressure during hypothermia and complete pulsus alternans was particularly apparent in one of the animals cooled by external ice packing. Although the observations were limited, it appeared that the decline in heart rate was not so profound in the externally cooled animals as in those animals cooled by the central venous method. The maintenance of a relatively high heart rate during external cooling may have been partially caused by heat generated by the flowmeter probe adjacent to the right atrium which, in the absence of cooling of the central blood stream, resulted in a selective warming of the region of the sinoatrial node. Fig. 2 illustrates observations made on an externally cooled dog just before and after the appearance of complete alternans. At a heart temperature of 30°C. (Fig. 2A) the rate of contraction, duration of systole, and isometric relaxation were all prolonged (*see legend*) and isometric relaxation was incomplete before the rise in isometric pressure began. The large a and c waves of the atrial pressure curve reflected vigorous atrial contraction against the incompletely relaxed ventricle. Fig. 2B illustrates observations made 30 seconds later after the appearance

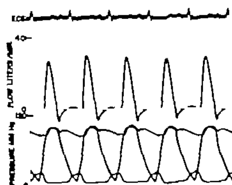


Fig. 2A. Pressure and flow observations before and after appearance of complete pulsus alternans. ECG and flow and pressure recordings of dog cooled externally to heart temperature of 30°C. HR, 133 per minute. MAP 91.4 mm. Hg. MLAP 7.0 mm. Hg. SV 4.1 ml. CO 545 ml. per minute, DS, 0.26 sec. IR, 0.16 sec. Not incomplete relaxation brief period of ventricular filling, and augmented atrial contraction waves. (Time marker 0.2 sec.)



Fig. 2B. Pressure and flow observations before and after appearance of complete pulsus alternans. Observations made 30 second after tracing in Fig. 2A. HR, 133 per minute. MAP 91.8 mm. Hg. MLAP 5.0 mm. Hg. SV 8.58 ml. CO 570 ml. per minute DS 0.30 sec. IR 0.16 sec. Not incomplete relaxation prior to ineffective beat and atrial alternans discordant with ventricular alternans.

of complete alternans. Left ventricular temperature heart rate and aortic pressure were unchanged but a minor spontaneous fall in mean left atrial pressure from 7 to 5 mm. Hg occurred. Cardiac output was insignificantly changed after the onset of alternans. The stroke volume of the effective beat in the alternans couple was essentially double the ejection volume prior to the onset of alternans which resulted in an increased ejection period and duration of systole in the effective beat. Although the rate of isometric contraction was increased the duration of isometric relaxation remained prolonged in the effective beat, relaxation was incomplete and ventricular filling time was abbreviated prior to the ineffective beat. By contrast the end-diastolic pressure was low and ventricular filling time was increased after the ineffective beat. However the total minute filling time was unchanged before and after the onset of alternans. The augmentation of atrial contraction waves persisted after the appearance of alternans, but in addition atrial alternans, which was discordant with ventricular alternans, appeared.

The single fortuitous observation of the effect of slowing of the heart rate on pulsus alternans was made in the same externally cooled animal as in Fig. 2. During the period of cooling pulsus alternans was sustained for a period of roughly 20 minutes. As cooling progressed heart rate slowed and complete alternans changed to incomplete alternans. In Fig. 3A at which time the heart temperature was 26.5°C and the heart rate was relatively slow at 82 per minute the duration of systole (average 0.38 second) and isometric relaxation (average 0.23 second) were markedly prolonged. The aortic pressure was 85 mm. Hg stroke volume (mean) was 4.6 ml. and cardiac output was 377 ml. per minute. With additional cooling to 25°C (Fig. 3B) the heart rate slowed to 71 per minute. Left atrial pressure was unchanged. Although the duration of systole and isometric relaxation were further prolonged (0.46 and 0.26 second respectively) as a result of lower ventricular temperature filling time was actually increased by a slowing of the heart rate and pulsus alternans disappeared. The more adequate ventricular filling was reflected by an increase in stroke volume (6.1 ml.) cardiac output (433 ml. per minute) and mean aortic pressure (95 mm. Hg).

Alternation in the magnitude of atrial contraction waves which was discordant

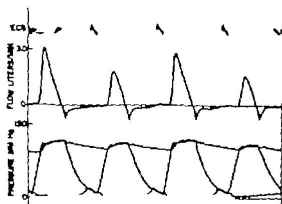


Fig. 3A The effect of spontaneous slowing of heart rate on sustained pulsus alternans. Heart temperature of 26.5°C HR 82 per minute SV (mean), 4.6 ml. CO 377 ml per minute MLAP 4.0 mm Hg MAP 85.0 mm Hg Note that pulsus alternans is present (Time marker 0.2 sec.)

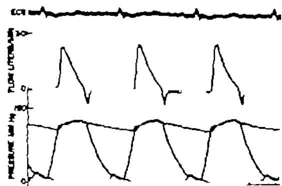


Fig. 3B The effect of spontaneous slowing of heart rate on sustained pulsus alternans. Observation made 7 minutes after Fig 3A at a heart temperature of 26°C. HR, 71 per minute SV 6.1 ml CO 433 ml. per minute. MLAP 4.0 mm Hg MAP 95.0 mm. Hg Note that pulsus alternans has disappeared

with ventricular alternans was a consistent finding regardless of the degree of alternation or the method of induction of hypothermia. Fig 4 illustrates an original tracing of complete alternans in which the sensitivity of the atrial pressure tracing was augmented Alternation in the magnitude of the "a" waves is apparent In addition alternation in the depth of the presystolic dip between the "a" and "c" waves is evident and reflects the alternation in end-diastolic ventricular pressure

II Effect of changes in left atrial filling pressure Observations were made on the effect of alteration in left atrial pressure in 2 dogs in which hypothermia was induced by cooling the venous blood and inducing tachycardia and sustained pulsus alternans by selective rewarming of the right heart. Fig 5A illustrates a tracing made during a representative experiment. At a left ventricular temperature of 30°C a heart rate of 143 beats per minute and mean left atrial pressure of 2.7 mm Hg complete pulsus alternans was evident. In Fig 5B the left atrial pressure was elevated to 6.3 mm Hg by infusion of blood and discernible alternation of ventricular and aortic pressures disappeared However as indicated by the flow tracing minor alternation in ejection volume remained When left atrial pressure was returned to the previous level complete ventricular alternans reappeared

III Effect of alteration in aortic outflow resistance Observations were made on 2 dogs cooled by venous-to-arterial pumping When blood was pumped via an extracorporeal circuit from the venous circulation into the arterial circulation the retrograde flow of blood from the pump against ventricular outflow resulted in the maintenance of a high mean aortic pressure an elevated end-diastolic aortic pressure and increased resistance to left ventricular outflow Atrial pressure was maintained constant

Fig 6A illustrates an observation made in an animal with a left ventricular temperature of 28.8°C during venous-to-arterial pumping Complete ventricular alternans was occurring at a heart rate of 128 per minute. Left atrial pressure was 7 mm Hg and mean aortic pressure was 102 mm Hg Duration of systole and isometric relaxation of the effective beat was obviously prolonged (0.28 and 0.16 second respectively) and the ineffective beat demonstrated the character of a beat resulting from reduced ventricular filling The stroke volume of the effective beat was 8.1 ml and cardiac output was 518 ml per minute.

Fig 6B illustrates the same animal after the cessation of venous-to-arterial pumping and adjustment of atrial filling pressure to 7 mm Hg Mean arterial pressure fell to 69 mm Hg Heart rate was essentially

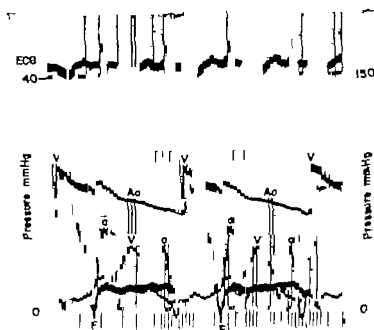


Fig. 4 Discordant atrial and ventricular alternans. Animal previously cooled by extracorporeal cooling of venous blood. Tracing made at heart temperature of 30°C. during rewarming and induced tachycardia. *a* waves of augmented left atrial pressure tracing (0-40 mm. Hg). *A* Aortic pressure (0-150 mm Hg). *V* Ventricular pressure (0-150 mm. Hg). *F* Aortic flow curve.



Fig 5A Effect of increased left atrial pressure on sustained pulsus alternans. Heart temperature, 30°C. HR, 143 per minute SV 6.3 ml. CO 450 ml. per minute. MLAP 2.7 mm Hg MAP 63.0 mm Hg. Left atrial pressure, 0-10 mm. Hg Aortic and ventricular pressure, 0-80 mm Hg (Time marker 0.2 sec.) Note complete ventricular alternans.

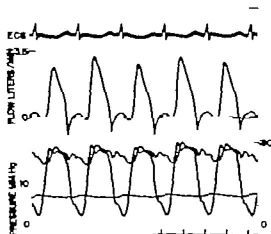


Fig 5B Effect of increased left atrial pressure on sustained pulsus alternans. Tracing made 1 minute after Fig 5A to increase left atrial pressure by infusion of blood. Heart temperature, 30°C. HR, 150 per minute SV (mean), 5.3 ml. CO 795 ml per minute. MLAP 6.3 mm. Hg MAP 83 mm Hg Note disappearance of discernible pressure alternans. Minor flow alternans persists.

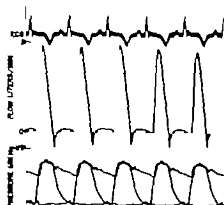


Fig 6A Effect of increased left ventricular outflow resistance on pulsus alternans Tracing made during venous-to-arterial extracorporeal cooling and pumping Heart temperature 28 8°C HR, 128 per minute. SV 8 1 ml CO 518 ml. per min to. MLAP 7.0 mm Hg MAP 102.0 mm Hg N to high end-diastolic aortic pressure and complet ventricular lternans. (Time marker 0 2 sec)



Fig 6B Effect of increased left entricula outflow resistance on pulsus alternans. Tracing made immediately after cessation of venous-to-arterial pumping (cf Fig 6A). Heart temperature 28 8°C. HR, 130 per minut SV 9.3 ml CO 1,209 ml. per minute. MLAP 7.0 mm. Hg MAP 69 0 mm. Hg Note fall in aortic pressure decrease in duration of contraction, and disappearance of ventricula alternans.

unchanged (130 per minute) Pulsus alternans disappeared The duration of systole was reduced to 0 24 second and isometric relaxation fell to 0 15 second The stroke volume (9 3 ml) exceeded the effective alternans beat, and cardiac output was increased to 1,209 ml per minute. The reinstitution of venous-to-arterial pumping immediately after this observation resulted in the recurrence of complete ventricular alternans.

Discussion

In 1917 Straub[8] stated that alternans develops only when the heart rate is so fast or the contour of the pressure curve so broad that the pressure does not have sufficient time to decline before the next ventricular excitation supervenes. Mitchell Sonnenblick and Sarnoff reached a similar conclusion on the basis of observations of pulsus alternans in isolated dog hearts, in situ innervated dog hearts, and isolated papillary muscle They noted that the weak beat could be accounted for on the basis of a shorter initial fiber length from which the weak beat was initiated and that the shorter fiber length was due to an inadequate period for diastole prior to the weak beat.

Sustained pulsus alternans has been noted to occur with extreme degrees of tachycardia[1] It is not difficult to visualize abbreviated filling time and incomplete relaxation as being instrumental in the development of pulsus alternans when the heart rate is unusually elevated but at more physiologic heart rates one would have to propose a prolongation of duration of contraction and/or relaxation in order for diastolic filling to be sufficiently brief or impaired to initiate ventricular alternation The previous studies of Berne[1] and D Amoto[12] have demonstrated that under hypothermia such a prolongation of systole and relaxation can occur and occupy a disproportionate portion of the cardiac cycle which may result in abbreviation of ventricular filling time. The present study as well as the observations of Berne have demonstrated that when heart temperature is reduced a severe reduction in stroke volume cardiac out put, and arterial pressure can occur at normal heart rates and minor degrees of

tachycardia as a result of reduction in ventricular filling time. It is during this period of altered contraction, slow relaxation, brief filling time, and reduced cardiac output that pulsus alternans occurs. Reversal of the abnormal contraction and relaxation by rewarming results in the disappearance of pulsus alternans and the return of stroke volume to normal without there being an appreciable change in heart rate. The occurrence of pulsus alternans was not noted by Berne in studies of increased heart rate induced by artificial stimulation of the atrium during hypothermia.[11] However, the degree of tachycardia induced, the method of measurement of cardiac output, and the methods of producing hypothermia in the present study are not comparable to those employed by Berne.

Although abbreviation of ventricular filling time as a result of alterations in heart rate and prolongation of systole and relaxation appears to be a critical factor in the production of alternation under hypothermia, it is not the sole cause since on occasion longer filling time was present during alternans under hypothermia than in the absence of alternans during normothermia (see Figs. 1A and 3A). Such an observation suggests that the altered dynamics of filling may play a significant role in the reduction of stroke volume and the appearance of alternation.

The role played by the relaxing myocardium in the dynamics of ventricular filling has been a subject of controversy. The concept of a "sucking" action by the rapid relaxation of the ventricle has been supported for many years by the observation of Katz[14] that a pressure gradient across the inflow orifice of the isolated turtle ventricle could be created by the relaxation of the ventricle. More recent support for the sucking action of the relaxing ventricle has been gained from the studies of Dodge, Hay, and Sandler[4] of the diastolic pressure-volume characteristics of the left ventricle in man. These investigators noted that in the early portion of diastole there was a short period during which ventricular volume increased while ventricular pressure was still falling. This observation is thought to be consistent with the hypothesis that the early portion of diastole is not an interval of entirely passive filling and that the elastic recoil of the ventricle plays a role in determining the pressure-volume characteristics of this portion of diastole. The striking reduction in the rate of isometric relaxation which extends into the diastolic filling period and obliterates the early diastolic dip characteristics of the diastolic filling period of the warm ventricle was a consistent finding during hypothermia. Thus, it appears that the enhanced filling by the rapid recoil of the ventricle is modified by cold and that the character of all or a significant portion of the diastolic filling period is determined in part by the rapidity by which the ventricle relaxes.

The change in the character of left atrial pressure also suggests that the distensibility characteristics of the diastolic filling period were altered by cold and delayed relaxation. The augmentation of atrial contraction waves during periods of abbreviated filling and incomplete ventricular relaxation was noted in all of the experiments. With the onset of ventricular alternans, alternation in magnitude of "a" waves which was discordant to ventricular alternans occurred. The augmentation of the "a" wave appears to reflect the accentuation of the pressure of atrial systole as a result of contraction against the resistance of an unrelaxed ventricle. After the appearance of ventricular alternans, the lower intraventricular pressure prior to the large or effective beat is reflected in a smaller "a" wave, whereas the incomplete relaxation prior to the ineffective or small beat results in an atrial systolic wave of even greater magnitude than that prior to onset of alternans. Atrial alternans in association with ventricular alternans has been recorded in man,[15] but it is not apparent from the illustrated recordings whether atrial alternans was discordant or concordant with ventricular alternans. Katz[2] noted alternation in intensity of atrial filling sounds in the presence of pulsus alternans in human beings. The atrial sound preceding the weak beat was more intense than that prior to the strong beat. One would expect the loudest filling sound to occur in that portion of the alternans couple offering the greatest resistance to ventricular filling. One could likewise postu

late that alteration in myocardial distensibility or compliance independent of abnormal relaxation may play a role in the alternation in intensity of heart sounds and in the genesis of alternans as it occurs in the diseased heart

The observations of Gleason and Braunwald on ventricular volumes in a single patient exhibiting postextrasystolic alternans are of interest with reference to the present observations on flow and pressure These investigators noted a smaller end diastolic volume from which the weaker beat originated and an increased duration of systole and systolic emptying of the strong beat Such an observation suggests that if similar dynamics are present in postextrasystolic alternans as in hypothermia the small diastolic volume after the stronger beat is the result of abbreviated filling time and incomplete ventricular relaxation and the increased strength and volume of the larger beat results from more effective relaxation of the ventricle after the weak beat

The studies of Friedman Daily and Sheffield have emphasized the importance of various factors which modify venous return and atrial filling pressure when pulsus alternans occurs in human subjects. Maneuvers which result in a decrease in atrial filling pressure such as passive tilting the application of venous cuffs and phlebotomy tend to induce alternation whereas transfusion and immersion which promote atrial filling have the opposite effect The observation that an increase in atrial filling pressure modifies or obliterates pulsus alternans under hypothermia suggests that the mechanism operative in man with heart disease is similar to that in animals subjected to cooling The observations suggest that when atrial pressure is increased pulsus alternans disappears as a result of enhancement of ventricular filling by the greater push of increased filling pressure partially overcoming the reduced distensibility of the cold ventricle.

Cooling of the myocardium by venous-to-arterial pumping provided a method whereby ventricular outflow resistance could be elevated in a constant manner The increased mean and end-diastolic aortic pressures augmented the prolongation of contraction and relaxation resulting from hypothermia and pulsus alternans in sustained form occurred during the cooling period When outflow resistance was reduced by cessation of venous-to-arterial pumping aortic pressure declined ventricular filling time was increased and alternans ceased

The high incidence of hypertensive heart disease in individuals with pulsus alternans [7] and the observation by Cooper Braunwald and Morrow that ventricular alternans occurs in a large percentage of patients with aortic stenosis, suggests that increased ventricular outflow resistance may frequently be a factor of importance in the genesis of alternans in human beings. On the other hand the present observations under hypothermia appear to be contrary to the observations of Friedman [4] who noted that in human subjects with sustained pulsus alternans, elevation of outflow resistance by the infusion of norepinephrine resulted in the disappearance of alternation However it is to be noted that in Friedman's illustrated experiment there was coincident slowing of the heart rate from 108 to 65 per minute with infusion of norepinephrine. If the mechanism of ventricular alternation in man is similar to that which occurs under hypothermia slowing of the heart rate alone could account for the disappearance of alternans even in the presence of increased outflow resistance

It is apparent from the studies presented that alternans as it occurs under hypothermia cannot be explained on the basis of one mechanism alone and that its occurrence is related to a complex of factors which are both myogenic and hemodynamic in origin It appears that in the hypothermic dog heart abnormal myocardial contraction and relaxation resulting in reduced and perhaps inefficient ventricular filling are essential to the occurrence of ventricular alternation The presence or degree of pulsus alternans under this condition is modified by other dynamic factors such as heart rate atrial filling pressure ventricular outflow resistance or a combination of these factors. Although the effect of these dynamic factors on pulsus alternans in hypothermic dogs is strikingly similar to that in man with heart disease one cannot conclude that a similar abnormality in myocardial contraction relaxation or distensi

bility is operative in pulsus alternans as it occurs in man. However in view of the observations of this investigation such a mechanism deserves strong consideration in future studies of pulsus alternans in man

Summary

Twenty two dogs were studied by simultaneous measurement of left ventricular pressure left atrial pressure aortic pressure and phasic aortic flow through the use of a square wave electromagnetic flowmeter The induction of hypothermia by extracorporeal cooling of blood or external ice packing resulted in reduced cardiac output and aortic pressure bradycardia and marked prolongation of duration of systole and isometric relaxation. In 9 dogs, selective rewarming of the sinus node during the period of hypothermia resulted in tachycardia a fall in cardiac output and stroke volume and the appearance of sustained pulsus alternans. During periods of ventricular alternation prolongation of systole and myocardial relaxation resulted in the abbreviation of ventricular filling time and varying degrees of incomplete ventricular relaxation Reversal of abnormal contraction and relaxation by rewarming of the left ventricle was accompanied by a return of stroke volume to precooled levels and disappearance of the alternation.

Two dogs cooled by external ice packing developed pulsus alternans during the cooling period In one of these animals a spontaneous slowing of heart rate during the period of progressive reduction in heart temperature resulted in increased ventricular filling time and disappearance of the pulsus alternans.

Elevation of left atrial pressure in 2 dogs with sustained pulsus alternans resulted in the disappearance of ventricular alternation without any appreciable change in heart rate

Increased ventricular outflow resistance produced by venous-to-arterial pumping during the cooling period was accompanied by pulsus alternans in 2 animals. Reduction of outflow resistance by cessation of extracorporeal pumping was accompanied by a fall in aortic pressure a reduction in duration of ventricular contraction and disappearance of pulsus alternans, even though the heart rate and left atrial pressure were unchanged

Prolonged myocardial contraction and relaxation resulting in abbreviated and abnormal character of ventricular filling are considered to be prerequisites to the occurrence of pulsus alternans at physiologic heart rates in the hypothermic dog heart. However the presence and degree of ventricular alternation is modified by other dynamic factors such as heart rate atrial filling pressure and ventricular outflow resistance.

REFERENCES

1 Traube L Ein Fall von Pulsus bigeminus nebst Bemerkungen über die Leberschwellungen bei Klappenfehlern und über acute Leberatrophie, Berlin. klin. Wchnschr 9 185, 1872.
2. Katz, L N and Feil, H. S Clinical observations on the dynamics of ventricular systole IV Pulsus alternans, Am. J M Sc 194:601 1937
3. Green, H D The nature of ventricular alternation resulting from reduced coronary blood flow Am J Physiol 114:407 1935.
4. Friedman, B Daily W M and Sheffield, R. S Orthostatic factors in pulsus alternans, Circulation 8:864 1953.
5. Wiggers, C. J Dynamics of ventricular contraction under abnormal conditions, The Henry Jackson Memorial Lecture, Circulation 5:321 1952
6 De Ison, A B J and Spencer M P A square- wave electromagnetic flowmeter for application to intact blood vessels, Circulation Res. 3:29 1955
7 Spencer M P and Denison, A B. J In Bruner H D editor-in-chief Methods in medical research, Chicago, 1960, Year Book Publishers, Inc Vol. 8, p. 333
8. Straub, J Dynamik der Herzalternans, Deutsch. Arch Klin Med 123:403 1917
9 Mitchell, J H Sonnenblick, E H and Sarnoff S J Pulsus alternans alternating end-diastolic fiber length as a causative factor Fed Proc 20 129 1961
10 Lewis, T The mechanism and graphic registration of the heart beat London, 1925 Shaw and Sons
11 Berne, R M Myocardial function in severe hypothermia, Circulation 2:90, 1954
12 D Amato, H E Cardiovascular functions in deep hypothermia In Dripps, R D editor The physiology of induced hypothermia, National Academy of Sciences—National Research Council Publication 451 pp 146-160, 1956
13 Katz, L N The role played by the ventricular relaxation in filling of the ventricle Am J Physiol 95:542, 1930
14 Dodge H T Hay R E and Sandler H Pressure volume characteristics of the diastolic left ventricle of man with heart disease Am Heart J 64:503 1962

15. DeRabago, P., Kohout, F. W., and Katz, L. N.: An unusual case of pulsus alternans recorded during cardiac catheterization from the pulmonary and systemic blood vessels, AM. HEART J. 49:472, 1955.
16. Gleason, W. L., and Braunwald, E.: Studies on Starling's law of the heart. VI. Relationship between left ventricular end-diastolic volume and stroke volume in man with observations on the mechanism of pulsus alternans, Circulation 25:841, 1962.
17. White, P. D.: Alternation of the pulse: A common clinical condition, Am. J. M. Sc. 150:82, 1915.
18. Cooper, T., Braunwald, E., and Morrow, A. G.: Pulsus alternans in aortic stenosis. Observations in fifty patients studied by left heart catheterization, Circulation 18:64, 1958.

An embryologic theory for ventricular inversions and their classification

Maria V. de la Cruz, M.D.
*Jorge Espino-Vela, M.D.***
*Fause Attie, M.D.***
*Luis Munoz C., M.D.****
Mexico City, Mexico

Reports on cases of corrected transposition of the great vessels (CTGV) have become frequent in the last few years,[1-4] a type of transposition characterized among other things by an *inverted position* of the ventricles, and recently also some reports have appeared of cases with inversion of the ventricles *without* transposition of the great vessels. It appears, therefore, that ventricular inversions are not rare, and it is our belief that they can be seen in combination with every type of truncoconal malformation—hence, our interest in analyzing the inversion of the ventricles anatomically and embryologically and correlating these data with a study of the development of the truncus-conus.

This paper presents an embryologic theory which intends to give an explanation for the development of ventricular inversions. It is supported by the classic concept that the heart originates from the fusion of two primordia, right and left, each one of which has different developmental potentialities. A classification of ventricular inversions is likewise presented which is based on the integration of that theory with the concepts of truncoconal malformations which one of us (M. V. C.) has advanced. We have divided ventricular inversions into two groups according to the visceral situs: ventricular inversions in situs solitus and ventricular inversions in situs inversus. Each group is subdivided into three subgroups according to the development of the truncus-conus with their corresponding varieties. The location of the cardiac apex is discussed in each type of visceral situs.

I. Normal development of the ventricles and the great vessels

The normal heart originates from two primordia, right and left, which unite in the midventral line and form a heart that has the shape of a straight tube. When this tube bends, the spatial position of the ventricles and their relationship with the atria are established. The partition of the truncus-conus, on the other hand, is responsible for the relationship between

From the Instituto Nacional de Cardiologia, Mexico, D.F., Mexico.
Received for publication July 29, 1966.
*Chief, Department of Embryology. Address: Department of Embryology, Instituto Nacional de Cardiologia, Avenida Cuauhtemoc N. 300, Mexico, D.F., Mexico.
**Chief, Department of Pediatric Cardiology.
***Assistant Research Fellow, Department of Embryology.
****Assistant Research Physician, Department of Embryology.

SITUS SOLITUS

Fig. 1. Diagrammatic representation of the ventral view of the heart of the human embryo. The shaded areas represent the structures which originate from the normal right cardiac primordium and the white areas represent those which originate from the left cardiac primordium. *A, B, C, D* and *E* represent different stages in the normal development of the heart according to Davis and Kramer. Figures *a, b, d* and *e* are diagrammatic representation of the hypothetical development of the heart according to the present theory showing different stages in the development of the ventricular inversion in a heart in situs solitus which may be normally situated ... terbolar sulcus left ... *Rt.* Atrioventricular ... cordis. *Vent.* Ventricle. *Rt.At.* Right atrium. *Lt.At.* Left atrium. *A. Chann.* Aortic channel. *Pl Chann.* Pulmonary channel. *Rt V.* Right ventricle. *Lt V.* Left ventricle. *C-V Fl.* Conoventricular flange. *A V Chann.* Conoventricular channel. *Rt.A V.O.* Right atrioventricular orifice. *Lt.A V.O.* Left atrioventricular orifice. *1.* Sinistroventral truncus ridge. *2.* Dextrodorsal truncus ridge. *3.* Dextroventral truncus ridge. *4.* Sinistrodorsal truncus ridge. *5.* Muscular portion of the interventricular septum. *I V C.* Inferior vena cava.

the great vessels and the corresponding ventricles.

A. Formation and torsion of the cardiac tube.[8]

1. STRAIGHT TUBE HEART. A canal-shaped myoepicardial mantle and its corresponding endocardial tube develop from each of the two primordia which give origin to the heart. When the ventral wall of the foregut develops, the right and left myoepicardial mantles unite with each other in the mid ventral line in a cephalocaudad direction, i.e., from above downward, and so do their respective endocardial tubes. This union is incomplete at the caudal end, by virtue of which each primordium gives rise to its corresponding atrium (Fig. 1,*A*). On the other hand, the remaining cavities, i.e., the aortic bulb (bulbus aorticus), the bulbus cordis, and the primitive ventricle, will have a right half and a left half originating from the right and the left primordia, respectively (Fig. 1,*A*). The cardiac cavities cephalocaudad wise will be the bulbus aorticus, the bulbus cordis, the primitive ventricle, and the atria (Fig. 1,*A*). They are separated from each other by a number of grooves: right and left interbulbar groove, right and left bulboventricular groove, and right and left atrioventricular groove (Fig. 1,*A*).

2. TORSION OF THE BULBOVENTRICULAR LOOP. The heart acquires a dorsal wall at the level of the right and left bulboventricular grooves, at which point it starts closing in both a cephalad and a caudad direction as far as the interbulbar and the atrioventricular grooves, respectively. This is why in the early stages of embryonic development the primitive ventricle and the bulbus cordis have a dorsal wall of their own, whereas the atria and the bulbus aorticus have not yet developed that structure. Once the dorsal wall appears, the dorsal mesocardium of the primitive ventricle and of the bulbus cordis develops. This mesocardium disappears when the torsion of the bulboventricular loop begins. Simultaneously, the left bulboventricular and the right atrioventricular grooves become deeper (Fig. 1, *B*). This results in the normal bulboventricular loop having a right-sided convexity and a left-sided concavity (Fig. 1,*C*). This structure actually consists of two limbs, one of which is cephalic and right-sided—the bulbus cordis—and the other caudal and left-sided—the primitive ventricle (Fig. 1,*C*).

While the left bulboventricular and the right atrioventricular grooves become deeper, the bulbus cordis, or future right ventricle, is placed farther and farther to the right, and the primitive ventricle, or future left ventricle, is placed farther and farther to the left (Fig. 1, *B*, *C*, *D*). Simultaneously with the frontal plane torsion, a sagittal torsion causes the right-sided bulbus cordis to be placed also anteriorly, while the left-sided primitive ventricle becomes left and posterior. Frontal and saggital torsions of the bulboventricular loop also cause the atria to remain cephalad and dorsal to the ventricles (Fig. 1,*D*). It should be emphasized that the atria are always placed in the same position: the right one on the right, and the left one on the left side (Fig. 1, *A* to *E*). Conversely, the position of the ventricles depends on the normal right convexity and left concavity of the bulboventricular loop (Fig. 1,*C*). The normal torsion of the bulboventricular loop is responsible for the right-sided location of the anatomically right ventricle and for its connection with the right atrium, as well as for the left-sided location of the anatomically left ventricle and its connection with the left atrium (Fig. 1, *C*, *D*, *E*).

The difference in the intrinsic anatomic architecture of the ventricles depends upon their different embryologic origin. The anatomically right ventricle derives totally from the bulbus cordis, whereas the anatomically left ventricle derives from the primitive ventricle and a portion of the conus, which is a part of the bulbus cordis (Figs. 1, *C*, *D*, *E*, and Fig. 2, *A*, *B*).

B. Formation of the ventricles and of the great vessels.[14] Kramer[14] in his studies on the partition of the truncus and the conus identified the latter as a part of the bulbus cordis which in turn becomes continuous with a new structure, the truncus arteriosus, derived from the bulbus aorticus (Fig. 1, *C*, *D*, and Fig. 2, *A*, *B*). The ascending portion of the aortic arch and the trunk of the pulmonary artery arise from the truncus. He established

forms the cephalic segment of the outflow chamber of *both* ventricles. The dividing line between the truncus and the conus is conventionally placed at the origin of the aortic and pulmonary sigmoid valve cusps.

Streeter,[1] continuing the work of Davis,[8] *found that the endocardial plate of the bulbus cordis gives rise to the trabecular zone of the right ventricle, whereas the same structure of the primitive ventricle gives rise to the trabecular zone of the left ventricle.*

In the 8.8-mm. size human embryo there is a ridge called the conoventricular flange (Fig. 2,A) placed opposite the primitive interventricular septum. The *presence of this ridge causes the conus* which gives rise to the outflow tract of both ventricles to remain on the right side of the primitive interventricular septum (Fig. 2,A). In older embryos the normal disappearance of the *conoventricular flange* permits the truncus-conus to shift leftward to the midline and the truncoconal septum to align with the primitive interventricular septum (Fig. 2,B). Thus one of the great vessels originates from the anatomically right ventricle and the other one from the anatomically left ventricle, which in this way acquires its *outflow* chamber (Fig. 2,B).

As the conoventricular flange disappears two inner longitudinal ridges appear over the entire length of the truncus and the conus. They have a *spiral arrangement in* a clockwise rotation of 180 degrees (Fig. 2,A). When they meet in the midline they form the spiral truncoconal septum which divides the truncus into the ascending portion of the aorta and the trunk of the pulmonary artery. They also divide the conus to form the infundibulum of the pulmonary artery and of the aorta (Fig. 2,B). If at this stage of embryonic development a relationship is established between the position of the aortic arches at the cephalic end of the truncus and that of the ventricle at the *caudal end of the conus*, it is apparent that in the cephalic end of the truncus the sixth aortic arch (the branches of the pulmonary artery) occupies a sinistrodorsal position, whereas at the caudal *end of the conus* the outflow chamber of the right ventricle is in a dextroventral position (Fig. 2,B). On the other hand, in the cephalic end of the truncus the *fourth aortic arch*, i.e., the horizontal segment of the aortic arch, occupies a dextroventral position, whereas the outflow chamber of the left ventricle at the caudal end of the conus is in a sinistrodorsal position (Fig. 2,B). *This spiral truncoconal* septum causes the branches of the pulmonary artery—sinistrodorsal—to communicate with the dextroventral infundibulum corresponding to the anatomically right *ventricle* (*Fig. 2,B*). *It also causes* the horizontal portion of the aortic arch—dextroventral—to communicate with the sinistrodorsal infundibulum which belongs to the anatomically left ventricle (Fig. 2,B).

The anatomic implications of this embryologic process are that (1) the pulmonary artery arises from the anatomically right ventricle in front of the crista supraventricularis, (2) the aorta springs from *the anatomically left ventricle, and* (3) the two great vessels cross each other normally.

When the truncoconal septum and the cushions of the atrioventricular canal align with the primitive interventricular septum the definitive interventricular septum develops. It is formed by the dextrodorsal and the sinistroventral ridges of the conus, by tissue originating from the dorsal and ventral cushions of the atrioventricular canal and from the primitive interventricular septum.

C. Position of the heart. Once the development of the bulboventricular loop is completed, the cardiac apex is oriented to the right. At about the ninth week of embryonic life it shifts to the left to occupy the fetal position, which is definitive.[7]

II. Theory on the Inversion of the Ventricles

The planes of future symmetry *are* established quite early in the embryo. Already in the straight tube heart stage there are two possibilities according to the future position of the body viscera. *In other words, there are two types of* hearts: those which will become a part of a situs solitus and those which will become a part of a situs inversus.

A. Situs solitus. As has been mentioned, the heart originates from the fusion of two primordia, a right one and a left one. Consequently, in the straight tube-like

heart the right half of the bulbus aorticus (truncus) the right half of the bulbus cordis, the right half of the primitive ventricle and the entire right atrium originate from the right primordium whereas the left half of these structures and the entire left atrium originate from the left primordium (Fig 1 *A* to *E*) *If there were an inversion of the developmental potentialities of the primordia so that the right primordium were provided with the potentialities of the left one and vice versa and if this disorder were to affect only the bulbus aorticus and the bulboventricular loop and not the atria* (*Fig 1,a to e*) *a developmental disorder would take place which would have the following features* (a) There would be an abnormal torsion of the bulboventricular loop causing an inversion of the ventricles, with the anatomically left ventricle placed on the right side and the anatomically right ventricle placed on the left side [8] (compare c, *d e* with *C D E* in Fig 1) (b) There would be a change in the truncoconal ridges in regard to their right and left positions (compare *d* and *e* with *D* and *E* in Fig 1) (c) The normal position of the atria would be preserved the right atrium on the right side and the left one on the left side in accordance with a situs solitus (Fig 1)

1 ABNORMAL TORSION OF THE BULBOVENTRICULAR LOOP (VENTRICULAR INVERSION) Should the right cardiac primordium have the features pertaining to the left one and vice versa, at the level of the bulbus cordis and of the primitive ventricle the following developments would take place in the bulboventricular and atrioventricular grooves The left bulboventricular groove which normally becomes deep would disappear and the right bulboventricular groove which normally disappears would become deep (compare *B* with *b* in Fig 1)

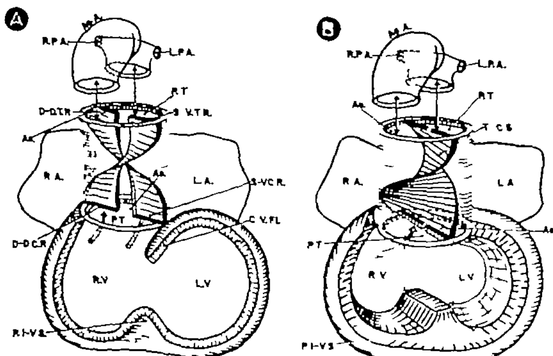


Fig 2 Diagrammatic representation of t[illegible] stages in the normal development of the truncus-conus of [illegible] human embryo Anterior [illegible] of the heart *A* Heart of an 8 8-mm embryo *B* Heart of 13 mm embryo ABBREVIATIONS *A A* Aortic arch *R.P.A* Right pulmonary artery *L.P.A* Left pulmonary artery *Ao* Aorta. *P.T* Pulmonary trunk *R.A* Right atrium. *L.A* Left atrium *C.V.Fl* Convoventricular flange. *R.V* Right ventricle *L.V* Left ventricle. *P.I.V.S* Primitive interventricular septum *T.C.S* Truncoconal septum. *D-D.T.R* Dextrodorsal truncus ridge *S-V.T.R.* Sinistroventral truncus ridge *D-D.C.R* Dextrodorsal ridge *S-V.C.R* Sinistroventral conus ridge

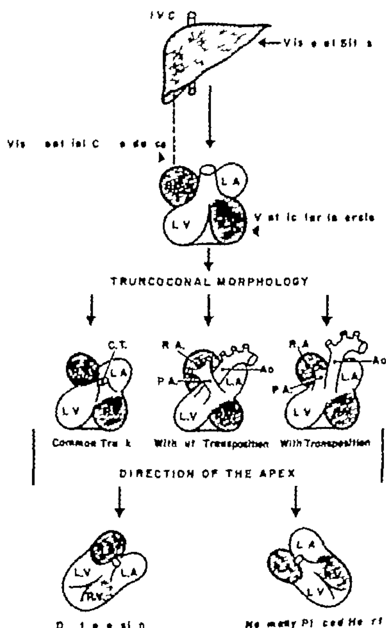


Fig. 3 Situs solitus. This diagram illustrates the basic elements which serve for the study and the classification of the ventricular inversions, i.e. the venoatrial concordance (or hepatoatrial concordance), on the one hand and the lack of correspondence of the position of the ventricles with the venoatrial situs, on the other. This diagram also illustrates *the three main types of truncoconal morphologies which accompany* ventricular inversions and, also, the position of the apex of the heart in relationship to the situs. ABBREVIATIONS: *I.V.C.*, Inferior vena cava; *R.A.*, Right atrium; *L.A.*, Left atrium; *L.V.*, Left ventricle; *R.V.*, Right ventricle; *C.T.*, Common trunk; *P.A.*, Pulmonary artery; *Ao.*, Aorta.

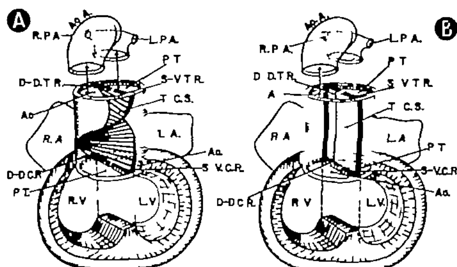
The left atrioventricular groove which normally disappears, would on the contrary become deep and the right atrioventricular groove which is normally deep would disappear (compare *B* with *b* in Fig 1) All of this would cause the bulboventricular loop to become concave on the right side and convex on the left side which is the opposite of the normal bulboventricular loop (compare *c* with *C* in Fig 1) The abnormal development of this bulboventricular loop would cause the bulbus cordis to be placed on the left side and the primitive ventricle on the right. This would inevitably lead to *a ventricular inversion* since the anatomically right ventricle (bulbus cordis) would be placed on the left side, and the anatomically left ventricle or primitive ventricle would be on the right side (Fig 1 *c d e*) Since the inversion of the right and left developmental potentialities takes place at the level of the bulbus cordis, the primitive ventricle, and the truncus, but *not* at the level of the atria these latter structures will develop normally the right atrium remaining on the right side and the anatomically left atrium on the left side (compare *a* and *e* with *A* and *E* in Fig 1) They will however connect with *spatially inverted* ventricles. Thus the anatomically right atrium will be placed *on the right* side and it will communicate with the anatomically left ventricle placed on the right side also whereas the anatomically left atrium placed on the left side will communicate with the *anatomically right* ventricle placed on the left side as well (Fig 1,*e*) As pointed out by Van Praagh the atria are in accord with the spatial position of the rest of the viscera, which in this particular case would be *an instance* of situs solitus (concordant visceroatrial situs) (Fig 3)

2. THE TRUNCOCONAL SEPTUM IN VENTRICULAR INVERSIONS. As has been mentioned the right half of the *truncus-conus* will have the features pertaining to the left half and vice versa (compare *e* with *E* in Fig 1) This will cause the truncal dextrodorsal ridge to become sinistrodorsal and the sinistroventral ridge to become dextroventral (compare *A* with *C* in Fig 4) At the conus the dextrodorsal ridge will become sinistrodorsal and the sinistroventral ridge will become dextroventral (compare *A* with *C* in Fig 4) Therefore, the truncoconal ridges are abnormally oriented as concerns their right and left orientations but not their dorsal and ventral orientations (compare *A* with *C* in Fig 4) These ridges may develop with an anticlockwise rotation of 180 degrees (Fig 4 *C*) or they may develop in a straight fashion (Fig 4,*D*) or they may not develop at all. Thus are originated the three groups of truncoconal cardiopathies which accompany ventricular inversions in situs solitus (a) ventricular inversions *without transposition of the great vessels* (b) ventricular inversions *with* transposition of the great vessels and (c) ventricular inversions with a common trunk (Fig 3)

a Truncoconal Septum With 180-Degree Anticlockwise Rotation (Ventricular Inversion in Situs Solitus Without Transposition of the Great Vessels) Should the truncoconal septum develop with an anticlockwise rotation of 180 degrees, the pulmonary artery will arise from the anatomically right ventricle, and the aorta *from the anatomically left ventricle* both vessels will cross each other However since an abnormal torsion of the bulboventricular loop takes place simultaneously the anatomically right ventricle will be placed *on the left side* and the anatomically left ventricle on the right side (Fig 1,*c* and Fig 4 *C*) The spiral development of the truncoconal septum (180 degrees) associated with an abnormal torsion of the bulboventricular loop (ventricular inversion) will cause the pulmonary artery to be *indirectly related to or connected with the left atrium (arterial atrium) placed on the left side by way of an anatomically right ventricle placed in a left sided position* the aorta will be indirectly related to or connected with the right or venous atrium placed on the right side by way of an anatomically left ventricle occupying a right-sided position (Fig 4 *C*) This arrangement is functionally comparable to a true transposition of the great vessels without actually being one Such an anatomicophysiologic picture should be adequately named *ventricular inversion in situs solitus without transposition of the great vessels*

b Straight Truncoconal Septum (Ven

SITUS SOLITUS WITHOUT VENTRICULAR INVERSION



SITUS SOLITUS WITH VENTRICULAR INVERSION

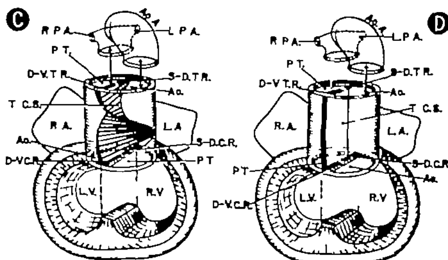


Fig. 4. Diagram illustrating the spatial position of the truncoconal ridges of hearts in situs solitus with normally placed or with inverted ventricles. *A*, Normally placed ventricles with spiral truncoconal septum. *B*, Normally placed ventricles with straight truncoconal septum. *C*, Ventricular inversion with spiral truncoconal septum. *D*, Ventricular inversion with straight truncoconal septum. ABBREVIATIONS: *A.A.*, Aortic arch. *R.P.A.*, Right pulmonary artery. *L.P.A.*, Left pulmonary artery. *A.*, Aorta. *P.T.*, Pulmonary trunk. *T.C.S.*, Truncoconal septum. *R.A.*, Right atrium. *L.A.*, Left atrium. *R.V.*, Right ventricle. *L.V.*, Left ventricle. *D-D.T.R.*, Dextrodorsal truncus ridge. *S-V.T.R.*, Sinistroventral truncus ridge. *D-D.C.R.*, Dextrodorsal conus ridge. *S-V.C.R.*, Sinistroventral conus ridge. *D-V.T.R.*, Dextroventral truncus ridge. *S-D.T.R.*, Sinistrodorsal truncus ridge. *D-V.C.R.*, Dextroventral conus ridge. *S-D.C.R.*, Sinistrodorsal conus ridge.

tricular Inversion in Situs Solitus with Transposition of the Great Vessels). Should the truncoconal septum develop in a straight fashion, a transposition of the great vessels will take place, i.e., the aorta will arise from the right ventricle in front of the crista supraventricularis, running ventral and parallel to the pulmonary artery. This latter vessel will arise in turn from the anatomically left ventricle. Because of the abnormal torsion of the bulboventricular loop, the anatomically right ventricle will be on the left side and the anatomically left ventricle on the right side (Fig. 1,*c* and Fig. 4,*D*). The development of a straight truncoconal septum is responsible for the transposition of the great vessels (Fig. 4, *B* and *D*) and the abnormal torsion of the bulboventricular loop determines the ventricular inversion (see Fig. 1,*c* and Fig. 4,*D*). Consequently, the aorta will be related to the left or arterial atrium placed on the left side through an anatomically right ventricle placed on the left and the pulmonary artery will be in relationship with the right or venous atrium placed on the right by way of an anatomically left ventricle situated in a right-sided position (Fig. 4,*D*). This arrangement is normal from the hemodynamic standpoint, although it is a true transposition of the great vessels. This anatomicophysiologic picture is usually known as corrected transposition of the great vessels. It should be named *ventricular inversion in situs solitus with transposition of the great vessels*.

c. Absence of a Truncoconal Septum (Ventricular Inversion in Situs Solitus With Common Trunk). If the truncoconal ridges do not develop, there will be no truncoconal septum and the heart will have only one vessel. This is currently known as persistent truncus arteriosus or common trunk. Because of the simultaneous abnormal torsion of the bulboventricular loop, the anatomically right ventricle is on the left side and the anatomically left ventricle is on the right side (Fig. 1,*c*,*d*). We may take as an example one of the types of truncus arteriosus, i.e., that in which this single vessel arises entirely from the anatomically right ventricle because of the ventricular inversion, this ventricle and the truncus arteriosus will be placed on the left and related to the left or arterial atrium also on the left side; on the contrary, the anatomically left ventricle will be placed on the right side and related to the right or venous atrium also placed on the right side. This malformation can be called *ventricular inversion in situs solitus with persistent common truncus arteriosus* (Fig. 3).

3. POSITION OF THE CARDIAC APEX. The developmental disorder which in a situs solitus leads to ventricular inversion with or without transposition of the great vessels or with a persistent truncus arteriosus may be seen in hearts with a right or a left orientation of the cardiac apex. The first group is that of dextroversion with ventricular inversion with or without transposition of the great vessels or with a truncus arteriosus (Fig. 3). The second group with a left orientation of the apex is a normally placed heart with ventricular inversion and with or without transposition of the great vessels or with persistent truncus arteriosus (Fig. 3).

B. Situs inversus. When in the very early developmental stages the right half of the embryo possesses the features of the left half and vice versa, the later development of the viscera will cause these to be in a mirror image arrangement of the normal visceral position, i.e., a situs inversus. This change in the planes of symmetry of the embryo will also affect the heart; hence, the right cardiac primordium will have the characteristics of the left half and vice versa (compare Fig. 5, *A* to *D* with Fig. 1, *A* to *D*). Such an alteration of the cardiac primordia would lead to the following features: (1) The right atrial primordium will be placed on the left side and the left one will be placed on the right (compare Fig. 5,*A* with Fig. 1,*A*), which in turn will cause the anatomically right atrium to be on the left side and the anatomically left atrium to be on the right side (concordant visceroatrial situs) (Fig. 5,*F*). (2) The bulboventricular loop will be concave to the right and convex to the left, which is the mirror-image of the normal bulboventricular loop in situs solitus (compare Fig. 5,*C* with Fig. 1,*C*). This determines a left-sided position of the anatomically right ventricle and a right

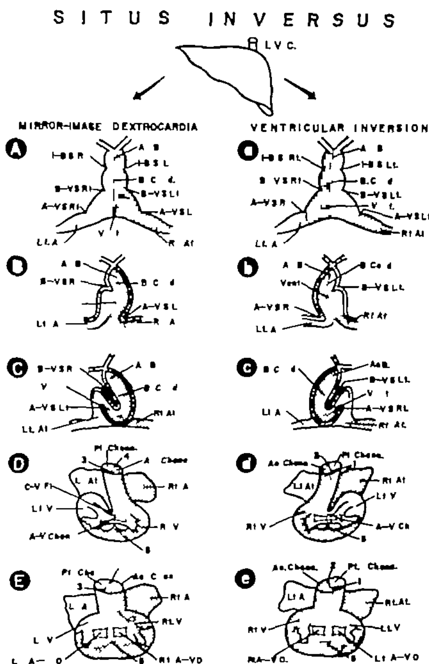
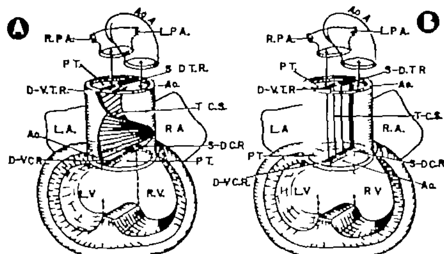


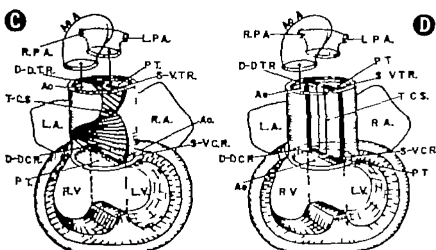
Fig. 5. Diagrams representing hypothetical stages in the development of the human embryonic heart according to the authors' theory. The shaded areas represent the structures which originate from the normal right cardiac primordium, and the white areas represent those which originate from the left cardiac primordium. *A, B, C, D* and *E* represent different stages in the development of the heart in mirror-image dextrocardia. Figures *a, b, c, d* and *e* represent different stages in the development of ventricular inversion in a heart in situs inversus which may be in mirror-image position or in levocardia. *(For key to the abbreviations see the legend to Fig. 1.)*

SITUS INVERSUS WITHOUT VENTRICULAR INVERSION



Without transposition of the great vessels (Normal Mirror-Image Dextrocardia) — With transposition of the great vessels

SITUS INVERSUS WITH VENTRICULAR INVERSION



Without transposition of the great vessels — With transposition of the great vessels

Fig. 6. This diagram is the mirror-image of the diagram in Fig. 4. It illustrates the spatial position of the truncoconal ridges of hearts in *situs inversus* either with normally placed or with inverted ventricles. *A*, Normally placed ventricles with a spiral truncoconal septum. *B*, Normally placed ventricles with a straight truncoconal septum. *C*, Ventricular inversion with a spiral truncoconal septum. *D*, Ventricular inversion with a straight truncoconal septum. (*For key to the abbreviations see the legend to Fig. 4.*)

sided position of the anatomically left ventricle (Fig 5 F) (3) The right half of the truncus and the conus will exhibit the features pertaining to the left side and vice versa (compare Fig 5 D with Fig 1 D)

Therefore the truncoconal septum will develop with an anticlockwise rotation of 180 degrees i e with a mirror image rotation as compared to normal (compare Fig 6 A with Fig 4 A) The pulmonary artery will thus cross the aorta anteriorly and from left to right and the aorta will cross behind the pulmonary artery from right to left. The final outcome is a heart in which the right chambers are placed on the left side and the left ones on the right and in which the great vessels cross each other in a mirror image fashion with respect to the normal heart (compare Fig 6 A with Fig 4 A) If its apex is placed on the right, a mirror image dextrocardia is constituted and it is a part of a situs inversus.

As has been mentioned in mirror image dextrocardia normally the right cardiac primordium has the potentialities of a normal left one and vice versa. *But it could happen that the developmental potentialities were inverted so that the right primordium had the potentialities of the right and the left one of the left primordium which is abnormal for a mirror image dextrocardia Furthermore this disorder might involve only the bulbus aorticus and the bulboventricular loop and not the atria* (Fig 5 a to e) Therefore a malformation would occur characterized by (a) an abnormal torsion of the bulboventricular loop leading to *ventricular inversion* with an anatomically right ventricle placed on the right side and an anatomically left ventricle placed on the left[1] (Fig 5 c d e) (b) a change in the truncoconal ridges in regard to their right and left positions (Fig 5 d e) (c) a normal position of the atria i e the anatomically left atrium remaining on the right side and the anatomically right atrium on the left, in accordance with a situs inversus (Fig 5)

1 BULBOVENTRICULAR LOOP The inversion of the developmental potentialities previously described at the level of the bulbus cordis and the primitive ventricle gives rise to a right-sided convex bulboventricular loop having a left concavity the features of which are opposite to those of a normal bulboventricular loop of mirror image dextrocardia (which is concave on the right and convex on the left side) (compare c with C in Fig 5) Consequently a normal bulboventricular loop for a normal heart in a situs solitus is *abnormal* for a mirror image dextrocardia (compare Fig 1 C with C and c in Fig 5)

This abnormal bulboventricular loop will determine the bulbus cordis to be placed on the right side and the primitive ventricle on the left side, which will inevitably lead to a *ventricular inversion* (Fig 5 c d e) This is so since the anatomically right ventricle (bulbus cordis) will be on the right side and the anatomically left ventricle (primitive ventricle) will be on the left side a completely abnormal arrangement of the ventricles for a mirror image dextrocardia (compare C with A in Fig 6)

Because inversion of the developmental potentialities affects only the bulbus cordis, the primitive ventricle and the truncus but *not* the atria these latter chambers will develop in the usual fashion seen in mirror-image dextrocardia i.e the anatomically right atrium will remain on the left side and the anatomically left atrium will *remain on the right side* (Fig 5) They connect, however with spatially inverted ventricles. In other words the anatomically right atrium on the left side connects with the anatomically left ventricle on the left side and the anatomically left atrium placed on the right side communicates with the anatomically right ventricle located also on the right (Fig 5 e) Therefore the atria follow the spatial position of the remainder of the viscera arranged in a situs inversus position (concordant visceroatrial situs) (Fig 7)

2 TRUNCOCONAL SEPTUM IN VENTRICULAR INVERSION Normally in mirror image dextrocardia the right half of the truncus-conus has the features of the left half and vice versa. In other words, the truncus-conus is also the mirror image of normal (compare Fig 5 D E with Fig 1 D E) However when *ventricular inversion* takes place in a situs inversus individual with mirror image dextrocardia the right and left halves of the truncus-conus will *also*

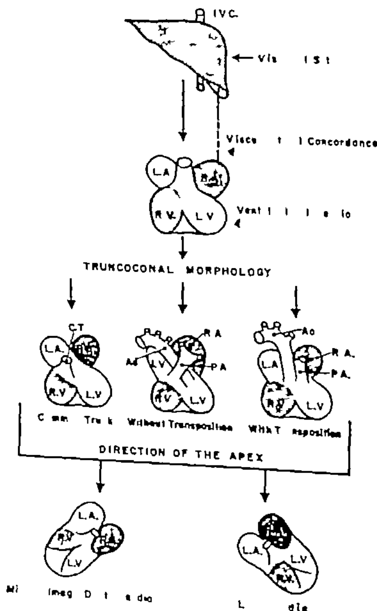


Fig. 7 Situs inversus. This diagram is the opposite of that in Fig 3. It also illustrates the elements which serve for the study and classification of ventricular inversions. Here, too, visceroatrial concordance is one of the diagnostic elements and the lack of correspondence of the ventricles with the visceroatrial situs is the other. Finally, this diagram also illustrates the three main types of truncoconal morphology which accompany ventricular inversion and the position of the apex of the heart in relationship to the situs. (*For key to the abbreviations see the legend to Fig 3.*)

have inverted potentialities as has been mentioned and the truncus- conus is *no longer* the mirror image of normal (compare Fig 5 *d e* with Fig 1 *D E*) On the contrary this structure is normal for a heart in situs solitus (compare Fig 5 *d e* with Fig 1 *D E*) but *very abnormal* for a mirror image dextrocardia (compare *d* and *e* with *D* and *E* in Fig 5) Therefore in the truncus the ridges will be dextrodorsal and sinistroventral as opposed to sinistrodorsal and dextroventral which is seen with normal ridges of mirror image dextrocardia (compare *C* with *A* in Fig 6) Similarly at the level of the conus the ridges are dextrodorsal and sinistroventral and not sinistrodorsal and dextroventral as expected in normal mirror image dextrocardia (compare *C* with *A* in Fig 6) Hence the truncoconal ridges will have the same spatial position as in a normal heart in situs solitus (compare Fig 6 *C* with Fig 4 *A*) but be abnormal for a mirror image dextrocardia (compare *C* with *A* in Fig 6)

These truncoconal ridges may develop with a clockwise rotation of 180 degrees (Fig 6 *C*) or they may be straight (Fig 6,*D*) or they may not develop at all Thus the three great groups of truncoconal cardiopathies accompanying ventricular inversions arise (a) ventricular inversion without transposition of the great vessels, (b) ventricular inversion with transposition of the great vessels and (c) ventricular inversion with a common truncus arteriosus (Fig 7)

a Truncoconal Septum With a Clockwise Rotation of 180 Degrees (Ventricular Inversion in Situs Inversus Without Transposition of the Great Vessels) If the truncoconal septum develops with a clockwise rotation of 180 degrees the pulmonary artery will arise from the anatomically right ventricle and the aorta from the anatomically left ventricle Both vessels will cross each other The presence of an abnormal torsion of the bulboventricular loop (ventricular inversion) (Fig 5,*c*) will cause the anatomically right ventricle to be on the right side and the anatomically left ventricle to be on the left side which is the opposite of the normal arrangement of mirror-image dextrocardia (compare *C* with *A* in Fig 6) Since the atria have not suffered any alteration of their developmental potentialities the anatomically right atrium will remain in a left-sided position and the anatomically left atrium in a right-sided position which is the expected situation in mirror-image dextrocardia (compare Fig 5 with Fig 6 *A* and *C*) Therefore the pulmonary artery will be indirectly connected with the anatomically left or arterial atrium placed on the right side by way of an anatomically right ventricle also placed on the right Likewise the aorta will be related to the anatomically right or venous atrium placed on the left by way of an anatomically left ventricle placed on the left side also (Fig 6 *C*) This condition behaves functionally as a transposition of the great vessels without being one and should be called *ventricular inversion in situs inversus without transposition of the great vessels*

b Straight Truncoconal Septum (Ventricular Inversion in Situs Inversus With Transposition of the Great Vessels) If the truncoconal septum arises in a straight fashion there will be a transposition of the great vessels, the anatomic features of which are an anterior and parallel aorta with respect to the pulmonary artery the aorta arises from the anatomically right ventricle in front of the crista supraventricularis and the pulmonary artery from the anatomically left ventricle Because of a simultaneous abnormal torsion of the bulboventricular loop (Fig 5,*c*) the anatomically right ventricle is on the right side and the anatomically left ventricle is on the left side (Fig 5 *d* and *e*) which is opposite to the normal arrangement in a mirror image dextrocardia (compare *D* with *A* in Fig 6) Consequently the straight development of the truncoconal septum is responsible for the transposition of the great vessels (compare *B* with *D* in Fig 6) and the abnormal torsion of the bulboventricular loop is responsible for the *inversion* of the ventricles (compare Fig 5,*c* with Fig 6,*D*) The atria on the other hand have not been involved and they remain in the mirror image position expected for this type of dextrocardia i e the anatomically right atrium is on the left side and the anatomically left atrium is on the right side (compare Fig

5 with Fig 6 *A* and *D*) Therefore the aorta will be in relationship with the left or arterial atrium by way of the anatomically right ventricle placed on the right side and the pulmonary artery will be related to the right or venous atrium through an anatomically left ventricle located on the left side (Fig 6,*D*) This arrangement is such that the heart behaves as a normal one from the standpoint of function although anatomically there is a transposition of the great vessels. This anatomico-functional condition is known as corrected transposition of the great vessels in a mirror image dextrocardia[9] and should be adequately called *ventricular inversion in situs inversus with transposition of the great vessels*

c. Absence of the Truncoconal Septum (Ventricular Inversion in Situs Inversus With Common Trunk) The absence of the truncoconal ridges will cause the heart to have only one vessel which is a condition known as persistent truncus arteriosus. Since there is at the same time an abnormal torsion of the bulboventricular loop (ventricular inversion) the anatomically right ventricle will be placed on the right side and the anatomically left ventricle will be placed on the left side (Fig 5 *c d e*) This is abnormal for a mirror-image dextrocardia (Fig 5 *C D E*) We may take as an example one of the types of persistent truncus, in which the vessel arises from the anatomically right ventricle. Because of the ventricular inversion the common trunk and the anatomically right ventricle will be placed on the right side and will be in relationship with the left or arterial atrium located on the right side of the heart. This, in turn, is the normal position of the atria in a mirror image dextrocardia. On the other hand the anatomically left ventricle placed on the left will be indirectly connected with the right or venous atrium located on the left side (Fig 7) This malformation could well be designated as *ventricular inversion in situs inversus with persistent truncus arteriosus*

3 LOCATION OF THE HEART APEX The developmental disturbance in a situs inversus leading to ventricular inversion with or without transposition of the great vessels or with persistent truncus arteriosus may be seen in hearts with a left or a right orientation of the cardiac apex The first case is none other than levocardia with ventricular inversion *with* or *without* transposition of the great vessels or with a persistent truncus (Fig 7) and the second case, in which the apex is directed to the right, is called mirror image dextrocardia with ventricular inversion *with* or *without* transposition of the great vessels or with a persistent truncus arteriosus (Fig 7)

III Classification of ventricular inversions

The theoretical concept according to which there may be an inversion of the developmental potentialities of the cardiac primordia right and left, which simultaneously affects the bulbus aorticus and the bulboventricular loop sparing the atria prompted us to propose an anatomic classification which includes the malformations caused by the disorders of those potentialities and also all the possible truncoconal malformations[3] (Table I)

Ventricular inversions are characterized by the fact that the spatial position of the ventricles does not correspond with the visceroatrial situs in which they appear in other words, the ventricles are *not* spatially oriented as they should be with respect to the atria and to the rest of the viscera Consequently there are two large groups of ventricular inversions one in which the heart is part of a situs solitus, and one in which it is part of a situs inversus.

Each type of *ventricular inversion* may be complicated by different types of truncoconal malformations. Each one of these in turn may be seen in either normally placed hearts or dextroversions for ventricular inversions in situs solitus. Finally it may be seen in either mirror image dextrocardia or levocardia for ventricular inversions in situs inversus.

All of these truncoconal malformations have been previously analyzed by one of us (M V C)[3]

Summary

1 A brief review of the formation and torsion of the cardiac tube and also of the development of the ventricles and the

Table I. Classification of ventricular inversions

Ventricular inversion	I. Situs solitus	1. With TGV	a. Isolated lateral position	Normally placed heart or dextroversion
			b. Isolated unequal partitioning at the expense of the aorta	
			c. Isolated unequal partitioning at the expense of the pulmonary artery	
		2. Without TGV	d. Lateral position plus unequal partitioning at the expense of the aorta	
			e. Lateral position plus unequal partitioning at the expense of the pulmonary artery	
		3. With common trunk	Lateral position	
	II. Situs inversus	1. With TGV	a. Isolated lateral position	Mirror-image dextrocardia or levocardia
			b. Isolated unequal partitioning at the expense of the aorta	
			c. Isolated unequal partitioning at the expense of the pulmonary artery	
		2. Without TGV	d. Lateral position plus unequal partitioning at the expense of the aorta	
			e. Lateral position plus unequal partitioning at the expense of the pulmonary artery	
		3. With common trunk	Lateral position	

TGV: Transposition of the great vessels.

great vessels in the normal human embryo is made.

2. An ontogenic theory is presented which explains ventricular inversions according to the following concepts: (a) Quite early in the developmental stages of the embryo the planes of symmetry are established. The right and left halves are endowed with peculiar potentialities which differentiate them from each other. These halves may be normally placed (situs solitus) or inverted (situs inversus). (b) The heart is originated by the fusion of two primordia, a right one and a left one. Each of the cardiac chambers, excluding the atria, will have one part which originates from the right primordium and another part which originates from the left primordium. In any particular situs it may happen that from the beginning there is an inversion of the developmental potentialities limited exclusively to the bulboventricular loop and the truncus. This will give rise to an inversion of the ventricles, which is expressed by the fact that the position of the ventricles does not correspond with the visceroatrial situs. Therefore there will be two types of ventricular inversions: one in situs solitus and one in situs inversus.

3 We propose a classification based on the integration of the concepts established for ventricular inversions with those of truncoconal malformations. In this classification we consider that for each type of ventricular inversion (in situs solitus or in situs inversus) there are three principal groups of truncoconal cardiopathies (1) those with a spiral truncoconal septum i.e., without transposition of the great vessels (2) those with a straight truncoconal septum i.e. with transposition of the great vessels, so called "corrected transposition of the great vessels and (3) those with absence of the truncoconal septum i e a common trunk.

The position of the apex in relation to the situs is also discussed.

REFERENCES

1 Anderson, R. C Lillehei, C. W and Lester R. G Corrected transposition of the great vessels of the heart A review of 17 cases, Pediatrics 20:626, 1957
2. Schiebler G. L., Edwards, J E., Burchell H B DuShane, J W Ongley P A and Wood, E H Congenital corrected transposition of the great vessels A study of 33 cases Pediatrics 27:851 1961
3 Honey M The diagnosis of corrected transposition of the great vessels, Brit. Heart J 25:313 1963.
4 Watson, G H. The diagnosis of corrected transposition of the great vessels, Brit. Heart J 26 770, 1964
5. Lev M and Rowaltt, U F The pathologic anatomy of mixed levocardia A review of thirteen cases of atrial or ventricular inversion with or without corrected transposition, Am J Cardiol 8:216, 1961
6. Anselmi, G., Muñoz, S., Machado, I Blanco, P and Espino-Vela, J Complex cardiovascular malformations associated with the corrected type of transposition of the great vessels, Am. H art J 66:614 1963
7 Van Praagh, R., and Van Praagh S Isolated ventricular inversion. A consideration of the morphogenesis, definition and diagnosis of nontransposed and transposed great arteries, Am. J Cardiol. 17:395 1966.
8. Davis, C. L. Development of the human heart from its first appearance to the stage found in embryos of twenty paired somites, Contrib. Embryol 19:245 1927
9 Goss, C. M Development of the median coordinated ventricle from the lateral hearts in rat embryos with three to six somites, Anat. Rec. 112 761 1952.
10. Yoshinaga, T A contribution to the early development of the heart in mammalia, with special reference to the guinea pig Anat. Rec 21:239 1921
11 Rawles, M E. The heart-forming areas of the early chick blastoderm, Physiol. Zool. 16:22 1943
12. De Haan, R. L. Organization of the cardiogenic plate in the early chick embryo, Acta Embryol. Morph. Exp. 6:26, 1963.
13 Copenhaver W M Heart, blood vessels blood and entodermal derivatives, Willier B H., et al. Analysis of development, Philadelphia, 1955 W B. Saunders Company
14 De la Cruz, M V and da Rocha, J P A ontogenetic theory for the explanation of congenital malformations involving the truncus and conus, Am. Heart J 51 782, 1956.
15 Kramer T C The partitioning of the truncus and conus and the formation of the membranous portion of the interventricular septum in the human heart, Am. J Anat. 71:343 1942.
16. Streeter G. L Developmental horizons in human embryos description of age groups XV XVI XVII and XVIII Being the third issue of a survey of the Carnegie Collection Contrib. Embryol 32 133 1948.
17 Licata, R. H The human embryonic heart in the ninth week, Am. J Anat. 94:73, 1954
18. De la Cruz, M V Anselmi, G Cisneros, F Reinhold, M Portillo, B., and Espino-Vela, J An embryologic explanation for the corrected transposition of the great vessels Additional description of the main anatomic features of this malformation and its varieties, Am. Heart J 57 104 1959
19 Van Praagh, R. Van Praagh, S Vlad, P and Keith, J D Anatomic types of congenital dextrocardia. Diagnostic and embryologic implications, Am. J Cardiol. 13:510, 1964

Case reports

Control of recurrent ventricular fibrillation by transvenous pacing in the absence of heart block

Henry T. Lew, M.D.
Harold W. March, M.D.
San Francisco, Calif.

The high incidence of ventricular arrhythmias as a cause of Stokes-Adams attacks in complete heart block suggests that extremely slow heart rates as such predispose to ventricular ectopic activity.[1] Electrical pacing of the heart at fixed rates in excess of the idioventricular rate is the most effective method of treatment for this complication.[2,3] It might then be supposed that slow ventricular rates resulting from depressed atrial pacemaker activity or atrial fibrillation with slow ventricular response, could also engender ventricular arrhythmias in the absence of complete A-V block and furthermore that pacing may be effective in an analogous way. Moreover, it is possible that electrical stimulation as such has a suppressive effect on arrhythmias.[3,4]

These latter considerations appear to be substantiated in the following case report. Multiple episodes of pharmacologically unresponsive ventricular tachycardia and fibrillation requiring repeated D.C. countershock were abolished permanently after a short term of transvenous pacing.

Case report

R. T. No. 324990437. This 70-year-old man was readmitted to the medical intensive-care unit from the vascular clinic where bigeminal rhythm had been detected. He had had myocardial infarction in 1965 at which time atrial fibrillation was first noted. Prior to this admission he had been taking digitoxin, 0.1 mg., tolbutamide 500 mg., and hydrochlorothiazide, 50 mg. daily. He had experienced palpitations, increasing angina pectoris, and edema during the previous 2 weeks.

Physical examination revealed bigeminal rhythm at a rate of 60 per minute. The cardiac apex was 1 to 2 cm. outside the mid-clavicular line in the fifth intercostal space. There were no murmurs and no gallops. The second sound was normally split, and pulmonic closure was not grossly accentuated. Bilateral basilar rales, hepatomegaly and edema of the legs were also noted.

The serum potassium was 4.2, sodium 140, chloride 109, and carbon dioxide 24 mEq. per liter.

Representative strips of electrocardiograms during the first 3 hospital days are shown in Fig. 1, A-C. They indicate atrial fibrillation, multifocal bigeminal rhythm, and short bursts of ventricular tachycardia.

The arrhythmia, originally ascribable to digitalis toxicity, was not abolished by 100 mEq. of potassium chloride or 100 mg. of diphenylhydantoin intravenously. There was transient suppression of the bigeminal rhythm on the second day with 200 mg. of quinidine four times a day. On the third day the patient complained of palpitations prior to a transient syncopal episode. The electrocardiogram showed atrial fibrillation with a slow ventricular rate and short run of ventricular tachycardia (Fig. 1,B). The dosage of quinidine was increased to 400 mg. four times a day. Two additional syncopal episodes occurred as a result of intermittent ventricular tachycardia (Fig. 1,C). An infusion of procaine amide (1 mg. per milliliter) suppressed the multifocal ventricular ectopic beats until the following day. The events of that day are presented in Table I.

It was by now evident that prophylaxis of the

From the Cardiopulmonary Section and Medical Service, Veterans Administration Hospital, San Francisco, Calif.
Received for publication June 27, 1968.
Address: Veterans Administration Hospital, Forty-second Ave. and Clement St., San Francisco, Calif. 94121.

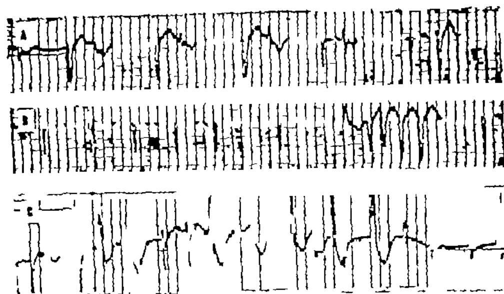


Fig. 1. Lead V A, Rhythm strip at time of admission, showing atrial fibrillation ith intermittent aberra t conduction and multifocal entricular ectopic beats in bigeminy. *B*, A short burst of ventricular tachycardia recorded during a transient syncope on the third day. *C*, Frequent entricular ectopic beats and a short run of entricular tachycardia preceding tw subsequent syncopal episodes.

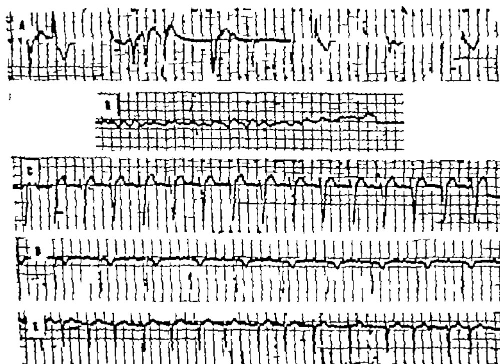


Fig. 2. Lead V A, Multifocal ectopic beats persisting after intravenous procaine amide. *B*, Ventricular fibrillation. *C*, Control of entricular tachycardia and fibrillation as achieved ith transvenous pacemaker, rate 90 per minute. *D*, Sinus rhythm with first-degree heart block as present immediately after termination of pacing. *E*, Atrial fibrillation recurred 13 days after pacing. Note the absence of ectopic beats with more rapid ventricular rate.

Table I

Time	Event	Treatment	Result
8.00 A M	Multifocal PVC*		
8 10	Syncope	External cardiac massage	Immediate resuscitation
8 15	Bigeminy with multifocal PVC (Fig 2 A)	1 400 mg of procaine amide intravenously	No effect
9 15	Bigeminy with multifocal PVC	60 mg of lidocaine intravenously	Ventricular fibrillation
9 16	Ventricular fibrillation (Fig 2,B)	Countershock	Immediate resuscitation, pH 7.49
9 20	Frequent PVC bigeminy	4 mg of propranolol intravenously	Brief suppression
9.35	Syncope ventricular tachycardia	External massage	Resuscitated
9 40		2 mg of propranolol intravenously	No effect
9 50	Ventricular fibrillation	Countershock	Resuscitated
10.25	Multifocal PVC	3 mg of propranolol intravenously	Brief suppression
10 35	Multifocal PVC	3 mg of propranolol intravenously	No effect
10 40	Ventricular tachycardia	Ceased spontaneously	
10 45	Multifocal PVC bigeminy	60 mg of lidocaine intravenously	Brief suppression
11 00	Bigeminy	40 mg of lidocaine intravenously	Brief suppression
11 10	Ventricular tachycardia	External massage 60 mg of lidocaine intravenously	Immediate resuscitation
12.00 P M	Ventricular fibrillation syncope	Countershock 30 mg of lidocaine intravenously	Immediate resuscitation
12.20	Ventricular fibrillation syncope	30 mg of lidocaine intravenously	Transient sinus rhythm with 2 1 block
12.50	Ventricular fibrillation syncope	Countershock	Resuscitated
1:00	Sinus bradycardia	0 5 mg of atropine intravenously	No effect
1 10	Ventricular fibrillation syncope	Countershock	Resuscitated
1.25	Ventricular fibrillation syncope	Countershock	Resuscitated
1 40	Ventricular fibrillation syncope	Countershock	Resuscitated

*Premature ventricular contractions

arrhythmias could not be achieved pharmacologically and that death from ventricular fibrillation would ultimately occur

At this point, a transvenous bipolar pacemaker was positioned in the right ventricle. During this procedure and before the catheter was appropriately placed in the outflow tract there were several recurrences of ventricular fibrillation requiring D.C. countershock. However as soon as pacemaker control of the heart was achieved, ectopic ventricular activity was abolished (Fig 2 C). The pacing rate was 90 per minute and the required battery current was 3 Ma. Pacing continued for 66 hours. At the end of the sixty-sixth hour P waves were noted and when the battery was turned off sinus rhythm resulted. The heart rate was 60 per minute (Fig 2,D). The catheter electrode was finally removed 86 hours after placement Reversion to atrial fibrillation occurred 13 days later but no ventricular ectopic activity recurred. The patient was alive and well 5 months after being discharged from the hospital, at which time the electrocardiogram again showed atrial fibrillation There were no ectopic beats (Fig 2,E)

Discussion

This report establishes that ventricular bigeminy and recurrences of ventricular tachycardia fibrillation can be abolished by transvenous pacing at a fixed and suitable rate even in the absence of complete heart block. It is believed that this patient with atrial fibrillation and slow ventricular response was predisposed to ventricular ectopic rhythms and ventricular fibrillation by a mechanism analogous to that prevailing in arrhythmia prone patients with complete heart block. This patient had a P R interval of 0 28 second after his conversion to sinus rhythm and it is possible that during atrial fibrillation his slow ventricular response was due to impaired A V conduction but heart block in the conventional sense was not present. Rather it is believed that heart failure and poor myocardial function perhaps abetted by digitalis toxicity started a cycle of impaired conduction into the ventricles with bradycardia bigeminy and ventricular tachycardia-fibrillation Temporary pacing at a rate of 90 per minute improved myocardial function restored sinus

rhythm temporarily and eliminated ventricular ectopic impulse activity permanently.

This patient's situation was so tenuous that ventricular fibrillation in the course of his trip to the cardiac laboratory was a distinct hazard. Moreover, the threat to life conceivably could be so imminent that there simply is not enough time to perform placement of a transvenous pacemaker. In such instances a myocardial wire could be inserted transthoracically into the left ventricle at the bedside so that pacing could be achieved virtually without delay.

Summary

Temporary intracardiac pacing was successful in suppressing recurrent ventricular tachycardia and fibrillation in the absence of complete heart block. The ventricular ectopic activity was permanently abolished after the pacemaker catheter was removed and the patient made a complete recovery.

REFERENCES

1. Yuceoglu, Y. Z., Langer, M., and Dresdale, D. T.: Transvenous electrical pacing of the heart, Am. Heart J. 71:5, 1966.
2. Zoll, P. M., Linenthal, A. J., and Zarsky, L. R. N.: Ventricular fibrillation: treatment and prevention by external electric currents, New England J. Med. 262:105, 1960.
3. Zoll, P. M., and Linenthal, A. J.: Long-term electric pacemakers for Stokes-Adams disease, Circulation 22:341, 1960.
4. Sowton, E., Leatham, A., and Carson, P.: The suppression of arrhythmias by artificial pacemaking, Lancet 2:1098, 1964.
5. Heiman, D. F., and Helwig, J. J.: Suppression of ventricular arrhythmias by transvenous intracardiac pacing, J.A.M.A. 195:1150, 1966.

Emergency replacement of valves in endocarditis

Edward J. Hurley, M.D.
*Frederic L. Eldridge, M.D.***
*Herbert N. Hultgren, M.D.****
Palo Alto, Calif.

Bacterial endocarditis is not the threat to life that it was prior to the introduction of the antimicrobial substances, yet adequate treatment still depends upon the early diagnosis, isolation of the offending organism, and the proper antibiotic therapy. The extent of damage to cardiac structures is determined by the duration of the disease, resistance of the host, and the virulence of the organism. When rapid eradication of the infecting organism can be accomplished, only small degrees of valvular and myocardial damage occur. Occasionally, however, if an adverse combination of these factors exists, patients may initially present to the physician with severe heart failure and deteriorate early in the course of treatment.

Since the aortic and mitral valves are often the major sites of endocarditic injury, the therapeutic role of repair or substitution of valves is obvious but has been used largely in the late treatment of bacteriologically cured cases. Early in the disease it has been the hope that antibiotics and supportive care in the form of cardiac glycosides, diuretics, and salt restriction will allow the patient to survive until the infection has been cured and reparative surgery accomplished. However, even in recognized and treated cases of bacterial endocarditis the mortality may reach 40 per cent.[1]

There appear to be no reported instances of the aggressive use of surgery early in the course of bacterial endocarditis to improve hemodynamic function. The case presented here demonstrates the functional benefit of prosthetic valve replacement carried out 10 days after antibiotics were started for a *Streptococcus viridans* endocarditis; the operative procedure was performed because the deteriorating hemodynamic condition due to aortic insufficiency made it unlikely that the patient would survive until it could be known whether the infection had been cured.

Case report

M. C., a 24-year-old Irish-born man, was admitted to the Veterans Administration Hospital, Palo Alto, California, on Sept. 1, 1965, with the complaints of dyspnea and swelling of the ankles. In June, 1965, while serving in the armed forces, he had undergone extensive dental repair. On July 1, recurrent chills

From the Departments of Surgery and Medicine, Stanford University School of Medicine and the Veterans Administration Hospital, Palo Alto, Calif.
Received for publication June 24, 1966.
*Assistant Professor of Surgery, Stanford University School of Medicine; Chief, Section of Thoracic and Cardiovascular Surgery, Veterans Administration Hospital; Established Investigator, American Heart Association. Address: Stanford University School of Medicine, Stanford Medical Center, Palo Alto, Calif., 94304.
**Associate Professor of Medicine and Head, Division of Pulmonary Physiology, Stanford University School of Medicine; Chief, Medical Service, and Director, Cardiopulmonary Laboratory, Veterans Administration Hospital.
***Associate Professor of Medicine and Chief, Division of Cardiology, Stanford University School of Medicine; Consultant, Veterans Administration Hospital.

and syncopal ttack resulted in examination by base physician who discovered a cardiac murmur The presence of murmur was reconfirmed when the patient as discharged from the service on J ly 15. Between July 15 nd September 1, progressive fatigue norexia, and dyspnea developed nd the patient sought medical care Upon admission, ad ditional information included 1 week history of dry nocturnal cough that wakened the patient, bdominal tenderness i both upper quadra ts, and gain in weight despite poor appetite.

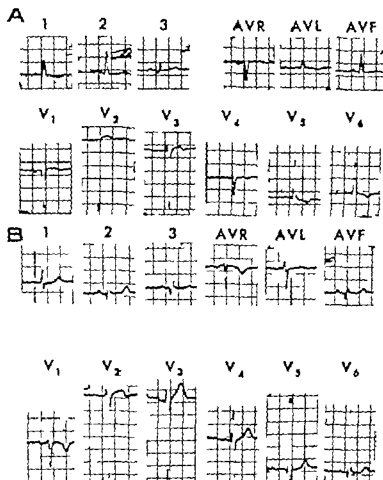
Physical examination revealed pallid young man whose temperature was 100.8°F pulse 104 respirations 22, and blood pressure 160 mm. Hg systolic nd 50 mm. Hg diastolic Marked bobbing of the head was present with pistol-shot sounds over the carotid and other peripheral arteries, capillary pulsations, and Durozier murmur N râles were heard over the lungs. There was regular cardiac rhythm, forceful left entricular heave, and an pical impulse 2 cm to the left of the midclavicular line. The ortic second sound was absent. A loud holosystolic murmur accompanied by an apical ystolic thrill, nd crashing decrescendo dia stolic murmur nd thrill were also found. Both murmurs ere maximal t the base but were well transmitted to the neck and apex. Localized to the apex as protodiastolic gallop and moderate rumbling mid-diastolic murmur Palpation of the abdomen revealed tender edge of the liver 5 cm. below the right costal margin, and an enlarged tender spleen. An Osler node was present in the right hand. There was moderate edema of the ankles.

Laboratory studies on the day of admission showed hematocrit 26 per cent hemoglobin 8 8 Gm. per 100 ml., white blood count of 5 400 with 92 per cent neutrophils (26 per cent band forms). Serum LDH was 330 units, blood urea nitrogen 16 mg creatinine 0.8 mg per 100 ml. sodium 136 mEq per liter chlorides 105 mEq per liter CO combining power 18 mEq. per liter and potassium 4 2 mEq per liter The A-G ratio was 2 1/2.6 Gm per 100 ml A negativ Coombs test, weakly positive latex fixation test, and negative test for cold agglutinins were found. An admission hest -ray film (Fig 1 A) showed enlargement of all four cardiac hambers, and evidence of pulmonary edema. An electrocardiogram (Fig 2,A) showed normal sinus rhythm, an xis of +40 degrees and abnormal T w ves not diagnostic of left entricular hypertrophy

Six samples of blood for culture were obtained on the day of admission. Because of the presumptive diagnosis of bacterial endocarditis, treatment with 20 million units of intravenous penicillin G and 1.5 Gm of streptomycin per day as started By the fourth day after admission, all six cultures of blood grew *Streptococcus viridans* sensitiv to penicillin tetracycline, chloramphenicol, colistimethate sodium, erythromy in and sodium methicillin 1.5 Gm. of sodium methicillin every 4 hours was added to the timicrobial regimen. With bed rest, restricted intake of sodium, and the administration of digitalis, there was initial improvement w th loss of eight of 10 pounds, decrease in dyspnea, and loss of ankle edema. However on the fifth hospital day all of these symptoms became worse the patient temperature rose to 104°F the pulse



Fig 1 A Chest film obtained on admission There is gross cardiomegaly nd pulmonary congestion *B* Chest film taken 6 da after admission. Cardiac enlargement and progression of the pulmonary congestion t fra k pulmonary edem is evident. *C* Chest film 4 months after second valv replacement. Diminution in heart size nd the return normal of pulmonary vasculature has occurred.



F g. 2. A. Elect ocardiogram taken on admission, Sept. 2 1965. B. Ele trocardiogram taken on March 25 196(4 months fter the second operation.

increased t 140 per minute, moist ales appeared throughou the chest, nd frank frothy pulmonary edema developed on several occasions. Supporting evidence of pulmonary edema was gain found on the -r y film (Fig. 1,B). Arterial blood gases revealed pH of 7.34 pCO_2 of 29 mm. Hg pO_2 of 69 mm. Hg and a saturation of 91 per cent while the patient as breathing oxygen by nasal catheter A repeat hematocrit was 31 per cent, hemoglobin 7.2 Gm. per 100 mL, nd a whit blood cell ount of 22,000 th 94 per cent neutrophils. The blood urea nitrogen had risen to 37 mg. per 100 mL, SGOT as 830, nd the LDH w 2,900 There was gross albuminuria.

Although medical therapy for the heart f ilure was intensified, progressiv decline in the patient condition occurred, ith tachycardia severe tach ypnea, reappearanc of protodiastolic gallop sound, recurring pulmonary edema elevated systemic enous pressure mental confusion and I bility t mov from itting position. Because of this rapid cardiac decompensation a direct surgical attack on the aortic alve as considered t be mandatory in spite of the short period of treatment of the endocarditis. On Sept. 10 1965 10 days fter institution of ntimicrobial therapy the patient w subjected t operation

The heat was opened through a sternal-splitt g incision. W th the use of rotating-disc oxygenator and mild hypothermia cardiopulmonary bypass as inst tuted The heart was grossly enlarged There was dilation of the scendi g aorta. A promi nent diastolic thrill was felt t the aortic root. The ascending aorta was ross-clamped, and topical cold saline solution was used t protect the heart during the period of anoxia. After aortotomy the remna ts of tricuspid aortic alve were found. There as complet disruption of all three sinuses of Valsalva The only poi ts of ttachment of the aortic val leaflets ere t the commissures. There were gelatinous egetations in the residual annulus, together with exophy tic mass of vegetation about the left coronary ostium. The errucous formation in the noncoronary sinus extended down onto the surface of the aortic leaflet of the mitral val Two deep-burrowing abscess sinuses were found. One extended I to the myocardium beneath the commissure sepa rating the right and left cusps. The second sinus

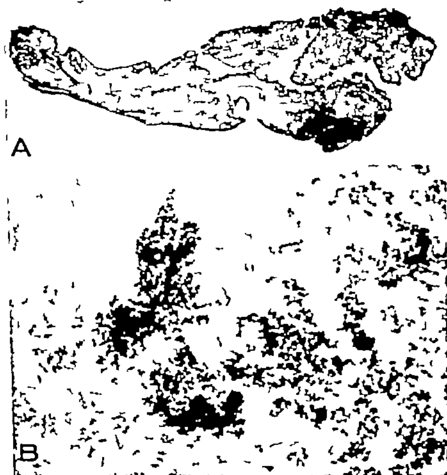


Fig. 3.A. Microscopic appearance of excised aortic leaflet, showing disruption of normal architecture and inflammatory response (EVG stain, ×8). *B*, Section of aortic leaflet with clumps of gram-positive bacteria (Gram stain, × 720)

beneath the left coronary ostium and had separated a small segment of the mitral annulus from the myocardium. The aortic valve leaflets and vegetations were excised and a No. 12 Starr-Edwards aortic prosthesis* was substituted. An attempt to close the abscess centers was made but the tattered mitral annulus was reinforced. The heart was allowed to fill and the aortic clamp removed after 64 minutes of cardiac anoxia. Defibrillation was accomplished and bypass discontinued. An elective tracheotomy was performed at the termination of the procedure, and the patient was returned to the Intensive Care Unit. During the next few days the patient did well, with complete disappearance of pulmonary congestion and symptoms referable to heart failure. Twenty-four hours after the operation the chest tube was removed and the patient was started on Coumadin sodium. After removal of the tracheostomy tube on the third postoperative day, ambulation was begun.

*Edwards Laboratory, Santa Ana, Calif.

Microscopic sections of the valve revealed acute and chronic inflammation believed to be of approximately 3 weeks duration (Fig. 3,A). Clumps of gram-positive bacteria were present (Fig. 3,B). Cultures of the valvular tissue removed at the time of operation were sterile. Antimicrobial therapy was continued in the original manner for an additional week. Intravenous sodium methicillin was administered for an additional 2 weeks. Sodium oxacillin, 1 Gm. every 6 hours, was given orally for another 1 month. Numerous paired cultures of blood over the next 2 months were sterile.

Despite the patient's continued well being 4 days after operation, a faint diastolic murmur appeared at the left sternal border although the blood pressure was maintained at 125 mm. Hg systolic and 75 mm. Hg diastolic. On October 8, 28 days after operation, the aortic diastolic murmur had changed from a faint blow to a moderately loud decrescendo murmur and the blood pressure had changed to 130 mm. Hg systolic and 50 mm. Hg diastolic. Although signs of aortic insufficiency had

returned the patient was asymptomatic and without complaints. Chest x-ray films taken in December 1965 revealed slight increase in cardiac size over that of the immediate postoperative period. The aortic diastolic murmur was now even more obvious. Because of the reappearance of the diastolic murmur and other signs of malfunction of the prosthesis, the patient was reoperated upon on Dec 8 1965 at which time exploration of the aortic valve was carried out again with the aid of cardiopulmonary bypass. The second operation revealed that the valve had been displaced from the aortic root because of the disruption of one third of the sutures in the area of the former commissure between the right and noncoronary sinuses. The remainder of the valve sewing ring was solid and well healed. There was no evidence of active infection. The previously noted sinuses were endothelialized but remained present as deep indentations into the subcoronary aortic root. The original prosthesis was excised and a No. 11 Starr Edwards aortic prosthesis was easily sutured in position. The reduction in the size of the valve was necessitated by the intense scarring that had occurred in the subcoronary area. The patient was discharged 3 weeks after operation with diminution in heart size. He has since returned to normal full-time physical activity. The last electrocardiogram and chest x-ray film are shown in Figs. *2 B* and *1 C* respectively. The electrocardiogram has become essentially normal for a 24-year-old man.

Discussion

Because of the well known delays which often attend the establishment of the diagnosis of bacterial endocarditis uncontrolled cardiac decompensation due to valvular damage coronary or peripheral embolization or overwhelming sepsis may lead to the death of the patient in spite of intensive medical care. Surgical intervention soon after cardiac decompensation becomes apparent should be able to alter the outcome however its use has been sporadic and usually withheld until there has been assurance of sterilization of the blood stream and stabilization of the patient's condition. Such an approach although perhaps leading to minimal surgical morbidity and mortality does not afford salvage of the patient who is progressively deteriorating. The case presented demonstrates that early operative intervention can be successful when a rapidly declining course due to endocarditic infection of the aortic valve has occurred. Because of the patient's clinical condition the repeated bouts of pulmonary edema and the possibility of vegetative embolization to a coronary or peripheral artery[2] it was thought that further delay was not justified even though there was no assurance that the aortic valve had been sterilized.

At the time of operation these problems became even more apparent. There were gelatinous soft vegetations about the coronary orifice on the left. These vegetations had already extended from the aortic valve down onto the mitral leaflet. All such vegetations were removed in order to reduce the possibility of postoperative embolization to a vital structure. Involvement of the mitral valve was superficial and simply required reinforcing sutures in the aortic leaflet in order to prevent disruption of the valve substance. Abscesses were present with extension into the myocardium. However visualization of these areas of destruction of the aortic root failed to show evidence of aneurysmal formation or imminent perforation with a subsequent aorticocameral fistula.

The possible danger of bacterial infection of the prosthetic valve was also well appreciated. However since the initiating infection was due to a penicillin-sensitive *Streptococcus viridans* and the patient had been under therapy for the previous 10 days the chance of secondarily infecting the inserted prosthetic valve was relatively small. In 1958 Tompsett and others showed that short term therapy of streptococcal endocarditis with penicillin and streptomycin for 14 days was successful in a majority of patients treated. Others[4] have noted a relapse rate of 6 per cent after 2 weeks of treatment. The case reported here revealed no evidence of streptococcal growth from the valvular tissue excised which indicates successful short term treatment of the patient's endocarditis, but the data on relapse rates show that such short term therapy would not always be successful in sterilizing a patient before emergency surgery such as that which we are proposing. Nevertheless, those individuals who present with rapidly decreasing cardiac function secondary to the endocarditis should not be withheld from surgery merely for the sake of assurance of bacteriologic sterilization. Until additional evidence is found we contend that the presence of a possibly active infection should not delay operation if the hemodynamic condition warrants surgical intervention.

The complication that did occur, disruption of the aortic suture line of the prosthetic valve, indicates that a less-than-favorable situation for suture placement does exist in the early stage of bacterial endocarditis. This argues against rash intervention in individuals with endocarditis who suffer minimal hemodynamic disturbances. However, the ultimate outcome in this case and the salvage of the patient clearly indicates that, despite the second operation, the initial valve substitution was lifesaving.

It should be pointed out that surgical treatment of endocarditis is not entirely new. As early as 1940, Touroff[5] undertook the division of an infected patent ductus arteriosus as a definitive and curative procedure. Kay and his colleagues[6] successfully cured a patient with *Candida albicans* endocarditis, which had not responded to amphotericin B, by removal of fungal vegetations. More recently, other surgeons [7,8] have approached the cure of bacterial endocarditis on cardiac valves after prolonged but ineffective intermittent antimicrobial therapy by excision of the valve and replacement with a prosthetic device. To our knowledge, the present case represents the earliest surgical intervention for hemodynamic difficulties secondary to endocarditis.

Summary

This is a case report on a 24-year-old man with *Streptococcus viridans* endocarditis that produced rapid circulatory deterioration because of massive aortic insufficiency. In order to prevent death from cardiac failure, early operative intervention became mandatory prior to absolute assurance that the endocarditis was controlled.

Prosthetic valve replacement was carried out 10 days after the institution of antibiotic therapy. In spite of the short period of therapy, sterilization of the aortic remnants was evidenced by the lack of bacterial growth in culture and the failure of the prosthesis to become infected. The result of the initial operation was a dramatic improvement in clinical and hemodynamic status.

The need for a second operation was based on the return of mild symptoms of aortic insufficiency and evidence of malfunction of the prosthesis. The lack of adequate fixation of the first ball valve was due to a failure of the sutures to remain embedded in the edematous and friable aortic annulus. Sufficient healing and scar formation permitted successful replacement of the initial valve at the time of the second operation without further morbidity. At the time of this writing, the follow-up period had been 12 months and the patient had returned to full activity without symptoms.

REFERENCES

1. Uwaydah, M. M., and Weinberg, A. N.: Bacterial endocarditis—A changing pattern, New England J. Med. 273: 1231, 1965.
2. Geiger, A. J., and Durlacher, S. N.: The fate of endocardial vegetations following penicillin treatment of bacterial endocarditis, Am. J. Path. 23: 1023, 1947.
3. Tompsett, R., Robbins, W. C., and Berntsen, C., Jr.: Short-term therapy of streptococcal endocarditis, Am. J. Med. 24: 57, 1958.
4. Hunter, T. H., and Paterson, P. Y.: Bacterial endocarditis, DM: Disease-a-Month 1: 1, 1956.
5. Touroff, A. S. W., and Vesell, H.: Subacute Streptococcus viridans endarteritis complicating patent ductus arteriosus: recovery following surgical treatment, J.A.M.A. 115: 1270, 1940.
6. Kay, J. H., Bernstein, S., Feinstein, D., and Biddle, M.: Surgical cure of Candida albicans endocarditis with open-heart surgery, New England J. Med. 264: 907, 1961.
7. Wallace, A. G., Young, W. A., and Osterhout, S.: Treatment of acute bacterial endocarditis by valve excision and replacement, Circulation 31: 450, 1965.
8. Kennedy, J. H., Sabga, G. A., Fisk, A. A., and Sancetta, S. M.: Isolated tricuspid valvular insufficiency due to subacute bacterial endocarditis, J. Thoracic & Cardiovas. Surg. 51: 498, 1966.

Clinical pathologic conference

Ralph H. Riley, M.D.
Carlos Arnaz, M.D.
Rudi Schmid, M.D., Ph.D.
Klaus Ranniger, M.D.
Harvey Wolinsky, M.D.
Seymour Glagov, M.D.
Chicago, Ill.

History

A 6 ear-old h te businessman w well until October 1963 he he began t experienc dull, mid-epig stric pain immediately after ingestion of an solid or liq id food Ea h time the pa lasted 7 t 8 hou nd was unrelated t position Relief w obt ned by fasting or ith narcotics. Symptom of fullness nausea, and omit ng fter eating were present for 3 months prior t admission, nd the pa ient lost 40 pounds in the 9 month prior t admission A history of hematemesis melena jaundic pruritus, dark urine or light tool could be obt ned Examination t nother hospital center prior t admission revealed emotional problem nd ps hiatric treatment recommended. Subsequently several other physicians were consulted nd all ttributed the patient depression to recent reverses his business areer The patient had been displaced suddenly f om what he thought secure nd importa t position i business firm The pa t history included herniorrhaphy 4 ears ea lier The patient mother and brother had both died in their lat si ties of arcinoma of the olon

During the first admission t Billings Hospital in June 1964 -ray examinations rev aled nonfilling of the gall bladder lesser-curv tur gastric ulcer was seen t gast oscopy Preparation for ga t oscopy included injection of 15 mg of morphine sulf t which was followed by pain i the right upper quadrant of the abdomen with bsent bowel sounds, fever nd leukocytosi Free ir in the peritoneal sac ould not be demon trated Acut holecystitis and gallstones were found t operation that night nd a holecystostomy nd tube dr inage ere carried out without incident The surgeon had the impression that neither gastric neoplasm nor gastric ulcer was present. T nsient disorientation nd ment l depression were the only complications of the postoper ti period The patient w dis harged on n ulcer regimen and was to be read mitted 6 eeks f r definitiv surgery

At home pai in the right upper quadrant per sisted for the next 2 eeks, despit adequat dr inage from the gall bladder A T-tube holangiogram showed no evidence of obstruction of the biliary duct but the patient as readmitted fter lamping of the t be i tensified the pa n in the right pper quadr nt.

Physical examination At the time of his final admission the patient w emaciated. The pulse te w 83 per minut nd the blood pressure as 90/48 mm. Hg The respiratory rat wa 30 per min te, and the temperature was 36 7°C The hest was hyperresonant nd diffuse heezing wa heard on uscult tion The right upper quadra t of the bdomen wa tender but no rebound or referred pain as present. Bowel sound were present the holecystostomy tube was functioning, nd no enlargement of the li er or spleen detected.

Laboratory examination Serum elect olyt con centr tions er ithi accepted normal limit Serum calcium was 9 6 mg per ent and serum phosphorus as 3 8 mg per cent. F ting blood sugar w 78 mg per cent serum albumin was 4 1 Gm per cent nd globulin as 1 1 Gm. per ent. Serum alkaline phosphatase bilirubin, amylase nd blood urea nitrogen values were ithin normal limits. The hematocrit level as 41 per cent nd the hit blood count 15,050 cells per cubic millimeter there wa 88 per cent polymorphonu-

With the part ipation of Jerry Petrovich, M.S. and Richard J. Jones, M.D.

The Conference was arranged and directed by Seymour Glagov, M.D.

From the Departments of Pa hology and Medicine Universi of Chicago, Chicago, Ill.

Received for publication Aug 1 1966.

*Work done during the tenure of an Established Investigatorship of the American Heart Associa ion Address Department of Pathology University of Chicago 950 East 59th St Chicago, Ill 60637



Fig. 1. Abdominal roentgenogram made 9 days after final admission demonstrates distention of small and large intestines.

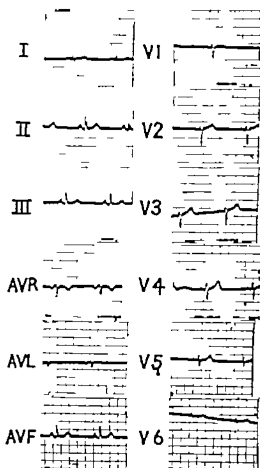


Fig. 2. Electrocardiogram in June 1964 is similar to subsequent tracings. The rate is 60 per minute, the P-R interval is 0.16 second, and isoelectric S-T segments are present in Leads V, V, and V.

clear leukocytes in the differential count. Cultures of bile, sputum, and urine were positive for Aerobacter species, but blood cultures were negative. The stool gave a positive test for occult blood. The serologic test for syphilis was negative. Urinalysis revealed no abnormalities.

X-ray examination. The abdominal examination (Fig. 1) made on the ninth day of the final admission demonstrates distention of the small and large intestines up to the mid-portion of the descending colon. The findings are those of paralytic ileus.*

Electrocardiographic examination.† The electrocardiogram (Fig. 2) taken during June 1964, is very similar to later tracings. The heart rate is 60 per minute, and sinus rhythm is present. The duration of the P-R interval is 0.16 second and isoelectric S-T segments are present in Leads V, V, and V.

Hospital course. On admission the patient complained of pain in the right upper quadrant. During the first 3 days he improved on treatment with nasogastric suction, antibiotics, and intravenous fluids. Fever and pain and tenderness in the left lower quadrant then developed but relief with nasogastric suction and parenteral fluids again resulted in improvement within 3 days. Oral feedings later produced pain similar in intensity and localization to that which he had experienced earlier in October 1963. After the patient became afebrile gastroduodenal x-ray examination and cholangiography were performed; no abnormalities could be demonstrated. Achlorhydria (with Histalog stimulation) was noted. Fever and pain in the right upper quadrant developed again 2 weeks after admission. Chest x-ray examination disclosed pneumonia in the right upper lobe; improvement was noted after treatment with penicillin and chloramphenicol. Starting on the patient's fifth day of hospitalization, frequent stools mixed with blood-tinged mucus were noted. This new development was accompanied by cramping abdominal pain. Stool cultures this time were positive for Aerobacter, Proteus, and *Streptococcus faecalis* organisms. Apnea and hypotension suddenly developed 3 days later and the patient died despite resuscitative measures.

*Dr. Jerry Petasnick.
†Dr. Richard J. Jones.

Discussion

DR. SCHMID. This 6 year-old man had a 9-month history of severe mid-epigastric

pain The pain was dull and constant and was aggravated by the intake of food Also eating produced a sensation of fullness, nausea, and vomiting Relief of these symptoms could be obtained from narcotics or by fasting It is probably important to note that he had no hematemesis melena jaundice or pruritus. His pain must have been quite severe because in addition to requiring narcotics for relief he stopped eating Allegedly because of this he lost a total of 40 pounds I suspect that this impressive loss of weight not only may have been due to the withholding of food but also may have had something to do with his underlying disease He was admitted to another hospital center for a thorough diagnostic examination but no organic disease was found and a psychiatric diagnosis was suggested This undoubtedly means that at that time the patient s disease whatever its nature had not yet progressed to a stage at which it could be detected by the available diagnostic methods.

In June 1964 he was admitted to Billings Hospital for another thorough examination and at this time two abnormal findings were discovered First his gall bladder failed to be visualized and second gastroscopy revealed an ulcer on the lesser curvature of the stomach Before the significance of the nonfilling gall bladder and the ulcer could be evaluated the patient forced the issue by developing acute cholecystitis which required immediate surgical attention It is quite likely as the protocol states, that this acute cholecystitis was precipitated by the 15-mg dose of morphine administered in preparation for the gastroscopy It is well known that morphine has a spastic effect on the sphincter and I assume that this precipitated the acute episode At operation the gall bladder and the surrounding tissues were inflamed and gallstones were present. A cholecystostomy with external drainage was performed and the patient improved. I am inclined to believe that the acute cholecystitis was an incidental episode not directly related to the underlying disease of this patient There are a few points in relation to the operation however which I think merit discussion

First the patient had an acute abdomen and a transient ileus although the gall bladder had not perforated This certainly may occur but I wonder whether there wasn t some underlying abnormality in the abdomen or bowel which facilitated the development of ileus. Second although only limited exploration was done the surgeon thought that no other abdominal disease was present. One can certainly be misled by simple palpation of the viscera during a surgical procedure but it seems to be significant that no evidence for an ulcer or carcinoma was found in the stomach Moreover there were three x-ray examinations of the upper gastrointestinal tract, and no ulcer could be demonstrated which suggests that the gastric ulcer seen on gastroscopy was quite superficial This possibility is supported also by the absence of significant bleeding for the hematocrit was stable and the gastric aspirate contained no blood Third during the postoperative period the patient had episodes of hallucination and disorientation We must remember that earlier at the other hospital center a psychiatric diagnosis was made and that later in the course of the disease the patient again required psychiatric attention This suggests that he may have had some sort of involutional depression unrelated to the underlying disease. The history does not permit the diagnosis of an organic disease of the central nervous system Hypoglycemia would seem to be unlikely also and although Addison s disease may be associated with abdominal pain and depression the presence of normal serum electrolyte concentrations throughout the course of the disease and during the stress of operation would tend to rule out adrenal insufficiency Fourth after operation the bile was drained to the outside. The tube drained quite well for 2 weeks, although the pain in the right upper quadrant persisted A cholangiogram was obtained which fully visualized the duct and the dye passed freely into the gut without evidence of obstruction. Yet when the tube was clamped there was a distinct increase in the pain in the right upper quadrant. The only explanation that I can think of is that there was some pathologic process in the small bowel which was irritated by the flow of bile similar to

the manner in which food was found to exacerbate the symptoms

Early in July 1964 the patient was admitted again to the University of Chicago Hospitals because of increased pain in the abdomen first in the right upper quadrant and later in the mid-epigastrium This pain was relieved somewhat by gastric suction but was aggravated by the intake of food as had been the case during the preceding 9 months. There was a transient episode of pain in the left lower quadrant associated with fever and a similar episode of more severe pain in the right upper quadrant, again associated with fever The patient was otherwise afebrile. The various laboratory reports and x-ray films do not help to explain these painful episodes It is particularly noteworthy that repeated determinations of serum amylase transaminase bilirubin and alkaline phosphatase were essentially normal Obviously the abdominal pain was the hallmark of the patient's disease and we should perhaps center on this aspect in trying to decide what he may have had.

Because of the pain in the right upper quadrant one could think of a hepatic process as the cause of the pain this could be due to a rapidly increasing parenchymal hepatomegaly producing stretching of the liver capsule a primary or metastatic neoplasm or single or multiple liver abscesses. All of these seem to be remote possibilities however because the liver was not palpably enlarged the conventional liver function tests were essentially normal jaundice was absent and the patient was afebrile Hepatoma may produce liver pain in the absence of jaundice but the normal alkaline phosphatase the only slightly elevated retention of Bromsulphalein and the normal size of the liver are not in line with this diagnosis. I find it difficult to conceive of a liver abscess which in the course of 9 months would not have produced chills and fever and would not have ruptured into adjacent structures. I notice that the bile grew Aerobacter but this probably represented secondary invasion after the insertion of the tube

Pain in the right upper quadrant calls also for consideration of the extrahepatic bile ducts. Could it be a carcinoma of the gall bladder the bile ducts, or the head of the pancreas? I think that these are rather unlikely because jaundice the cardinal manifestation of these lesions, was absent the bile ducts were patent and no evidence of malignancy was found on exploration Moreover carcinoma of the gall bladder tends to metastasize early to the liver which should result in hepatomegaly Finally carcinoma of the head of the pancreas although producing jaundice is not usually associated with severe abdominal pain Indeed jaundice is entirely painless in some of these patients, although it seems to me that tenderness and at times frank pain in the right upper quadrant is not uncommon

A third possibility is a primary lesion of the stomach Could it be carcinoma of the stomach? Again this seems to be unlikely for the following reasons there was no evidence of major hemorrhage three gastrointestinal series were normal palpation on surgery failed to reveal an indurated area and there was no enlargement of regional lymph nodes. It would be expected that in a process which has lasted for at least 9 months one or more of these findings would be present. On gastroscopy an ulcer was seen but for reasons discussed the ulcer appears to have been quite shallow I doubt that a gastric ulcer could have produced all of the manifestations in the course of this patient's disease However we must keep in mind that an ulcer was seen and we may have to discuss this again

A primary lesion of the pancreas is another possibility worth considering Diseases of the pancreas are notorious in presenting great diagnostic difficulties and there is little that distinctly characterizes the pain of pancreatitis But there are a number of points which militate against the diagnosis of chronic pancreatitis there was no diarrhea or steatorrhea there was no calcification of the pancreas, which is detectable in about half of the cases the serum calcium and amylase concentrations were normal the patient had neither back pain nor pleural effusion Carcinoma either of the body or of the tail of the pancreas may be a more likely possibility because it does not produce jaundice until late in its course The sam

is characteristically deep constant and boring and may be relieved by withholding food Loss of weight is almost always severe but fever intestinal hemorrhage and steatorrhea are frequently absent However this lesion tends to metastasize to the liver early and hepatomegaly elevated alkaline phosphatase or increased retention of Bromsulphalein occurs sooner or later in at least half of the cases. About 20 per cent of the patients have hyper glycemia or glycosuria amylase is moderately increased in about 50 per cent. In some instances gastrointestinal roentgenograms show frank displacement of the duodenal loop In addition carcinoma of the body of the pancreas is at times associated with thrombophlebitis or focal fat necrosis. Since none of these symptoms, signs or findings was present a neoplasm of the pancreas seems to be unlikely although it cannot be ruled out definitely It is noteworthy however that pancreatic carcinoma and psychiatric manifestations been associated in a number of reports depression has been particularly emphasized But this may be expected of a disease which produces such severe pain and is so difficult to diagnose I am nonetheless disinclined to ascribe this patient's psychological difficulties to a carcinoma of the pancreas.

A malignant or fibrotic process in the retroperitoneal space usually is associated with severe back pain displacement of the kidneys or psoas shadows and/or obstruction of the ureters. Furthermore one would expect that a lymphoma of this region would sooner or later lead to enlargement of mediastinal or supraclavicular lymph nodes. None of these manifestations was present

So far we have not considered the small bowel Adenocarcinoma or scirrhous carcinoma of the small bowel is quite rare, but if they do occur they are usually located in the duodeum or in the terminal ileum The most frequent manifestations include the triad of intestinal hemorrhage obstruction and perforation [1] Pain may be present but frequently it is mild and usually is overshadowed by one of the major complications. The patient's course does not appear to suggest this diagnosis.

A much more likely possibility is a sarcoma or lymphoma of the wall of the small bowel Lymphomas comprise approximately 40 per cent of all malignant tumors of the small bowel they occur more frequently in males than in females, and the peak incidence occurs at about 50 years of age.[1-4] The typical manifestations of these lesions are quite similar to those found in this patient Pain is usually severe and localized in the epigastrium or the right upper quadrant. It may be present for 6 to 18 months before the diagnosis is established The pain frequently mimics that produced by a peptic ulcer including the relief obtained by withholding food or the ingestion of milk or alkali Indeed the initial diagnosis is peptic ulcer in the majority of cases, and not until later in its course is the nature of the disease correctly recognized The pain is believed to be due to infiltration of the muscularis of the bowel producing irritation of the nerve plexus this may account for the fact that carcinomas of this organ are usually less painful but tend to ulcerate more frequently Anorexia nausea and vomiting are almost always present and loss of weight is severe. Functionally chronic obstruction of the small bowel is often seen but acute ileus rarely occurs. This is probably due to interference with intestinal motility by the lymphomatous process. It is tempting to assume that, in our patient, the administration of morphine not only precipitated the acute cholecystitis but also was responsible for the transient ileus of the diseased bowel Intestinal hemorrhage is infrequently seen and anemia is usually a late manifestation of this disease. Moreover detectable malabsorption or frank steatorrhea rarely occurs Fever is usually absent, and the white blood cell count commonly is normal. The viscus seldom perforates, and even if perforation has occurred the presence of a lymphoma may not be appreciated at the time of operation On the other hand intussusception often of transient nature may occur probably due to the disturbed motility and the tendency of the lymphoma to produce polypoid growths protruding into the intestinal lumen. I consider the two episodes of increased abdominal pain which occurred during the terminal phase of this patient's disease

to be consistent with the diagnosis of transient self reducing intussusception.

One would think that lymphoma of the small bowel should be easily demonstrable by x-ray examination but this is rarely the case.[3] Such studies frequently fail to reveal abnormalities and at best give only suggestive evidence of nonspecific chronic obstruction or rigidity of the bowel wall.

The pathologic process frequently appears to have begun in the mucosal lymphatic plaques. From there the lymphoma spreads in either longitudinal or annular fashion through the muscularis at times lifting up the covering mucosa and producing polypoid protrusions. Physical examination frequently fails to yield positive findings a palpable mass, representing either a tumor or matted or distended intestinal loops, is found in only about one third of the patients. Hepatosplenomegaly is conspicuously absent On the other hand the lesion may extend to the adjacent large bowel or stomach In the stomach it may produce giant rugae polyps, or superficial ulcerations. It is distinctly possible that our patient s superficial gastric ulcer may have been related to lymphomatous involvement of the gastric wall not as a primary lesion but by extension from the small bowel

Thus, I believe that lymphoma of the small bowel is the diagnosis most consistent with th manifestation and course of this patient s disease The terminal event may have been a necrotizing enteritis with septicemia and shock the administration of broad-spectrum antibiotics may have been a contributing f tor I am well aware that the diagnosis of intestinal lymphoma is arely mad during life and therefore I do not hesitate to pursue my speculative diagnosis even further So fa we have paid l ttle attention to laboratory investigations bec use they generally seem to be of l ttle help in this particula diagnosis There is one laboratory finding however which caught my fancy A single glol ulin determ nation was reported as 1 1 Gm per cent which suggests that the gamma globul n le el mu t have been quit low In cons lering lymphoma, I could n t h lp thinking of Hodgkin disease which is known to be associ ted with defective antibody formation. Hodgkin s disease of all the lymphomas of the intestinal tract, most frequently involves the duodenum and the adjacent parts of the stomach wall and diagnosis by x-ray examination appears to be most unreliable. I am putting forth this additional diagnosis merely as speculation fully realizing that it is based on a single laboratory determination which may be of doubtful significance

The symptoms and findings certainly were not suggestive of an aneurysm Partial arteriosclerotic occlusion of the celiac artery producing insufficiency of the mesenteric arteries is a possibility but the duration of the patient s disease the absence of detectable malabsorption and the lack of a distinctly positive test for blood in the stool would render this diagnosis less l kely Patients with mesenteric insufficiency sooner or later have acute arterial occlusions and n view of this patient s severe pain I would have expected this to have happened during the early phase of his disease

DR ARAOZ The autopsy was performed 2 hours after death The emaciated body weighed only 99 pounds and was 68 inches long the patient appea ed to be older than the stated age of 67 years No cholecystostomy tube was present at autopsy blood tinged fluid could be expressed from ncisional fistula which had conta ned the tube The peritoneal cav ty contained 300 c.c. of turb d red brown fluid f om which *Aerobacter aerogenes* and *Escher hia coli* were cultured *Escher chia ol* and *P oteu vulgaris* grew in cultures of blood from the right atrium The serosa of the dark red distended loops of small intestine was covered by fibrinopurulent exudate The wall of the jejunum (Fig 3) was nfarcted and had perforated The ent jejunum and ileum were friable and many intest nal loops were adherent to on another The intestinal infarction was a consequence of occlusion of both the superior mesenteric and celiac arteries An aneurysm 5 cm long and 6 cm n circumference was present n the abdominal aorta (Fig 4) A fresh thrombu (Fig 5) in the aneurysm occluded the orif ce of the celiac artery The thrombus was of recent orig n and its formation must have led to a marked



Fig 3 Microscopic appearance of the wall of the infarcted jejunum at the site of perforation. Ischemic changes and loss of structural detail is shown. Hematoxylin and eosin magnification, ×20.

sudden increase in intestinal ischemia Perforation of the jejunum was the final event and probably occurred approximately 70 hours before death The superior mesenteric artery was narrowed both by atherosclerosis and a recent thrombus. This thrombus probably formed about 10 days after the patient s second hospital admission accounting for the exacerbation of abdominal pain There was less organization of the thrombus than expected but the degree of organization depends on the condition of the wall of the vessel prior to thrombosis.[11,12] Organization of a thrombus is slower in the presence of intimal sclerosis, but ulceration complicating the intimal disease also provides a base for new thrombosis, which in this case subsequently occluded celiac and superior mesenteric arteries. The inferior mesenteric artery (Fig 6) was sclerotic and contained a partially recanalized thrombus. The location of the aneurysm and its gross and microscopic appearance are compatible with an arteriosclerotic etiology Additional findings included a superficial mucosal ulcer (0 8 cm in diameter) on the anterior wall of the body of the stomach and marked sloughing of colonic mucosa. The surgically excised fragment of gall baldder showed severe acute inflammation and autopsy revealed that the gall bladder was focally necrotic but not perforated

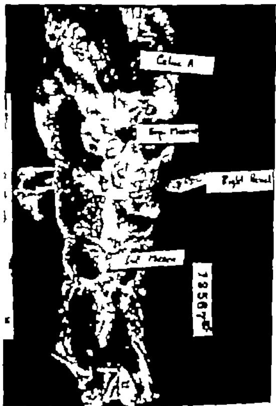


Fig 4 Opened abdominal aorta with aneurysmal dilatation. A thrombus occludes the ostium of the celiac artery a thrombus is lodged in the superior mesenteric artery nd the ostium of the inferior mesenteric artery is obliterated.



Fig. 5. Microscopic appearance of the aorta at the origin of the celiac artery. The arterial ostium is occluded by the thrombus in the aorta. The lumen of the celiac artery was already narrowed by organized thrombus and atherosclerosis. Hematoxylin and eosin, magnification ×20.



Fig. 6. Microscopic appearance of the inferior mesenteric artery showing arteriosclerosis and recanalization of old thrombus. Hematoxylin and eosin, magnification, ×20.

The right lung weighed 1,240 grams and showed gross and microscopic features of aspiration pneumonia. Focal necroses were seen in the myocardium; the heart weighed 330 grams. Except for a small cortical tubular adenoma, 1.0 cm. in diameter, in the right kidney, there was no evidence of neoplasia. Enlargement of lymph nodes was minimal and nowhere did microscopic examination indicate any lymphoid or reticuloendothelial abnormality.

Relationship between electrocardiogram and electrolytes

Borys Surawicz, M.D.
Lexington, Ky.

Electrocardiographic abnormalities caused by electrolyte imbalance may be classified as specific or nonspecific. The specific changes are attributed to the effect of the altered concentrations of ions on the transmembrane potentials of all cardiac cells. Such changes are usually reversible and their development and regression follow a predictable course.

The nonspecific electrocardiographic abnormalities may be caused by structural rearrangements of the myocardium produced by electrolyte imbalance. Degenerative lesions have been attributed to chronic deficiency of potassium or magnesium and other types of electrolyte imbalance.[1-4] Electrocardiographic abnormalities resulting from such anatomic lesions may be expected to reflect the topography and extent of the lesion rather than the nature of the agent producing the lesion. Not much information is available about electrocardiographic abnormalities caused by anatomic lesions due to electrolyte imbalance in man and therefore they will not be discussed further.

Relationship of electrocardiogram to transmembrane action potential

During the spread of excitation all myocardial fibers undergo rapid depolarization of the cell membrane. This results in a reversal of electrical charges between the inside and the outside of the cell followed by a slow repolarization and then by a period of recovery. The diastolic recovery period is different in the pacemaker and the nonpacemaker fibers. (In the nonpacemaker fibers of the atria and the ventricles the diastolic potential remains steady until the fiber is depolarized by the spread of excitation. In the pacemaker fibers, a continuous slow diastolic depolarization brings the transmembrane potential to a critical level of about −65 mv, which is called the threshold potential.) At this level the depolarization becomes rapid and gives rise to a spontaneous action potential (AP). The AP engenders electrotonic current which crosses the membrane of adjacent nonpacemaker cells, lowers their transmembrane potential to the threshold potential, and generates further depolarization.[5]

Fig. 1 shows a diagram of an atrial and a ventricular transmembrane AP superimposed on the electrocardiogram. The AP of the ventricular fiber has a longer duration than the AP of the atrial fiber. It is customary to divide the AP into five phases. Phase 0 designates the rapid upstroke; Phase 1, the short spike; Phase 2, the slow

From Cardiovascular Division, Department of Medicine, University of Kentucky College of Medicine, Lexington, Ky.
Aided by Research Grant HE 07359 from the National Institutes of Health, United States Public Health Service.
Received for publication Dec. 21, 1966.
*Professor of Medicine and Director, Cardiovascular Division, University of Kentucky College of Medicine.

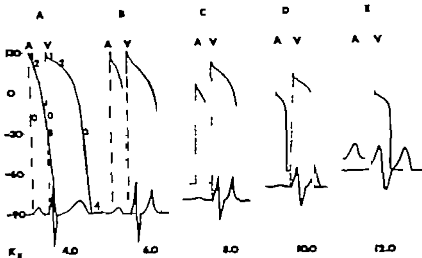


Fig. 1 Diagram of an atrial (A) and ventricular (V) action potential (AP) superimposed on the electrocardiogram. The numbers on the left designat the transmembrane potential in millivolts (mv) and the numbers at the bottom the extracellular concentration of potassium (K) in milliequivalents per liter I tracings A and B the resting membrane potential (RMP) is − 90 mv whereas the total amplitude of the AP is 130 mv because the upstroke overshoots the 0 potential by +40 mv Note the shortening of the AP the increased elocity of Phase 3 the progressiv decrease in the RMP and in the mplitude of the AP with increasing K. The most rapid upstroke of the AP is shown as line interrupted by wide spaces (A and B) the slowest upstroke is shown as continuous line (trial AP in E and ventricular AP in E). Note the decreasing upstroke elocity and the increasing duration of the QRS complex with increasing K_E I A and B the atrial and the entricular AP ha the same RMP and the same amplitude whereas in C and D the RMP of the atrial AP is less negativ than the RMP of the ventricular AP and the amplitude of the trial AP is lower than that of the corresponding entricular AP See text.

plateau like part of repolarization Phase 3 the more rapid repolarization and Phase 4 the recovery The magnitude of the membrane potential at rest is determined chiefly by the ratio of the intracellular to the extracellular concentration of potassium The normal rest g membra potential (RMP) of the atrial and ventricular fibers is about −90 mv (Fig 1) Depolarization and the reversal of charges is caused by the rapid influx of sodium nto the cell which is due to an increase in the permeability of the membrane to this ion. During Phase 2 the interaction of the membrane permeability to sodium and to potassium is such that th transmembrane potential does not change appreciably The more rapid Phase 3 is apparently initiated by an increased permeability to potassium, which causes a more rapid exit of this ion from the cell Depolarization and repolarization occur during sy tole, whereas the recovery (Phase 4) takes place in diastole. During this recovery phase the sodium ions which had entered the cell during excitation leave the cell, and the potassium ions return into the cell These ionic movements proceeding against the electrochemical gradient are attributed to the action of a hypothetical ionic pump which requires energy of the cellular metabolism

The electrical activity of the pacemaker fibers and the fibers of the conducting system cannot be recognized in the surface electrocardiogram probably because the tissue mass of these cells is too small and because they are too far from the body surface However changes in depolarization and repolarization in these fibers can affect the spread of impulses through the heart and give rise to a variety of arrhythmias and cond iction disturbances

The sum of all depolarization and re polarization of the atrial fibers is responsible for the origin of the P wave and the T wa e that of the ventricula fibers is responsible of the origin of the QRS complex S-T segment, and the T wa e The relationsh p between the entricular

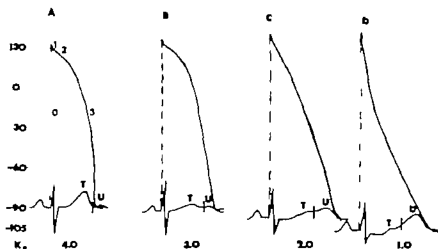


Fig. 2. Diagram of the ventricular AP superimposed on the electrocardiogram for extracellular concentrations of potassium (K) of 4.0 (*A*), 3.0 (*B*), 2.0 (*C*) and 1.0 (*D*) mEq./L. The numbers on the left designate the transmembrane potential in millivolts as in Fig. 1. The RMP, the amplitude of the AP and the overshoot of the control tracing (1) are the same as for the ventricular AP in the Fig. 1,*A*. Note the progressively increasing length of Phase 2, decreasing velocity of Phase 3, and increasing duration of the AP. Furthermore, note the progressive increase of the RMP (more negative), and the increasing amplitude of the AP. The electrocardiographic changes are described in the text.

complex of the electrocardiogram and the ventricular transmembrane AP has been studied in isolated rabbit hearts. Electrocardiographic patterns of electrolyte imbalance produced in the rabbit were nearly identical with the electrocardiographic patterns of electrolyte imbalance in man. Therefore one can make a reasonable assumption that the relationship between the electrocardiogram and the transmembrane AP observed in the rabbit and presented in Figs. 1 and 2 is applicable to man. The duration of Phase 0 is in the order of only a few milliseconds but the time required to depolarize all ventricular fibers represented by the QRS complex, lasts about 0.03 second in the rabbit and about 0.08 second in the adult man. In the absence of focal blocks in the conducting system, the duration of the QRS complex depends on the velocity of depolarization in the ventricles. The duration of the S-T segment corresponds approximately to the duration of Phase 2 and that of the T wave to the duration of Phase 3 of the ventricular AP. In the rabbit heart the duration of the Q-T interval is only slightly greater than the duration of the ventricular transmembrane AP recorded on the surface of the ventricle.[8] The slope of Phase 3 of the AP is usually similar to the slope of the terminal portion of the T wave. The end of the T wave coincides approximately with the end of the ventricular ejection, and the U wave is usually inscribed during relaxation. Abnormalities of the extracellular concentration of potassium and calcium produce the most specific changes in the shape and duration of the ventricular AP and the most characteristic electrocardiographic patterns.

Hyperpotassemia

An increased extracellular K concentration produces two changes in the transmembrane AP: (1) decreased duration of the AP and increased velocity of Phase 3, and (2) lowering of the RMP. The first effect is attributed to an increased membrane permeability to potassium[1] and the second to the decreased transmembrane concentration gradient of potassium. Fig. 1 *B* demonstrates that the effect on repolarization (Phase 3) occurs when the concentration of potassium is increased to 6.0 mEq./L. At this concentration the effects of a slight lowering of RMP are still not evident. The shortening of the ventricular AP and the increased slope of Phase 3 are probably responsible for the

shortening of the Q-T interval and the narrowing and peaking of the T wave. Peaking of the T wave is the earliest electrocardiographic manifestation of hyperpotassemia which occurs when the plasma K concentration exceeds 5.5 mEq./L., usually before the electrocardiogram shows any measurable alteration of the QRS complex.[11-13] The diagnosis of hyperpotassemia cannot be made with certainty on the basis of T wave changes alone. The characteristic tall, steep, narrow, and pointed T waves are present in only 22 per cent of patients with hyperpotassemia. In the remainder of the patients the tall T wave is very similar to tall T waves in patients with bradycardia, psychiatric disorders, cerebrovascular accidents, left ventricular diastolic overload, and subendocardial ischemia and in some individuals with no apparent abnormalities. When the tall peaked T wave is the only electrocardiographic abnormality produced by hyperpotassemia and the duration of the QRS complex and of the S-T segment is normal, the Q-T interval is either normal or decreased. Patients with tall T waves due to myocardial ischemia, cerebrovascular accidents, or left ventricular diastolic overload usually have a prolonged Q-T interval. The U waves in patients with hyperpotassemia are usually low or absent. Occasionally U waves may be simulated by a low T wave, particularly when the P-R interval is prolonged.

Fig. 1 *C-E* demonstrates that a progressive increase in the extracellular K concentration produces a progressive decrease in the RMP. This decreases the upstroke velocity of the AP, which in turn slows the intraventricular conduction and increases the duration of the QRS complex. Although the duration of the ventricular transmembrane AP remains decreased, the Q-T interval may be prolonged because of the increased duration of the QRS complex. If one corrects the Q-T interval for the prolonged QRS interval by subtracting from the Q-T the interval by which the QRS complex exceeds 0.08 second, one will find that the Q-T interval is usually not prolonged. However, in advanced hyperpotassemia, ventricular depolarization is very slow, large portions of the ventricular myocardium undergo repolarization before depolarization is completed, and the determination of the end of the QRS complex may be difficult or impossible (Fig. 1 *F*). In the presence of a pattern of advanced hyperpotassemia with a wide QRS complex, the T wave may lack its characteristic peaked and narrow configuration, probably because the T wave abnormalities secondary to intraventricular conduction disturbance obscure the primary T wave changes caused by the increased steepness of Phase 3 of the AP.

When the plasma K concentration exceeds 6.5 mEq./L., QRS changes are usually present. A correct electrocardiographic diagnosis of hyperpotassemia can usually be made in all cases in which the plasma K concentration exceeds 6.7 mEq./L. The uniformly wide QRS complex in hyperpotassemia differs from the electrocardiographic pattern of bundle branch block or pre-excitation because widening affects both the initial and the terminal portions of the QRS. The wide S wave in the left precordial leads frequently helps to differentiate a pattern of hyperpotassemia from a typical left bundle branch block, and the wide initial portion from a right bundle branch block. Occasionally, the wide QRS complex in patients with hyperpotassemia resembles the typical pattern of left bundle branch block.[4] With an increasing plasma K concentration the QRS duration increases progressively, and there is a rough correlation between the duration of the QRS and the degree of hyperpotassemia.

When the plasma K concentration exceeds 7.0 mEq./L., the P wave amplitude usually decreases and the duration of the P wave increases because of the slower conduction in the atria. The P-R interval is frequently prolonged as a result of slower atrioventricular transmission. When the plasma K concentration exceeds 8.8 mEq./L., the P wave is frequently invisible. When the QRS complex is wide, a low amplitude or absence of the P wave helps to differentiate the pattern of hyperpotassemia from intraventricular conduction disturbances of other origin. The disappearance of the P wave at the time when the ventricular complex is still well defined indicates that excitability of

atrial fibers is abolished at a lower K concentration than is the excitability of the ventricular fibers. Fig. 1 *C* and *D* shows that the resting membrane potential and the amplitude of the AP of the atrial fibers are more decreased than the resting membrane potential and the AP amplitude of the ventricular fibers. The electrocardiogram in Fig. 1 *C* shows a decreased amplitude and increased duration of the P wave. In Fig. 1,*D* the P wave is barely discernible whereas in Fig. 1 *F* the P wave is absent because the impulse produces no propagated response but only a small local depolarization in the atria. It is of interest that in the isolated preparations the pacemaker fibers continue to function after the atrial muscle fibers have become inexcitable.[30] The pacemaker may be displaced from the S-A node into the A-V node, bundle of His, or the Purkinje fibers. It has been shown that the impulse originating in the S-A node may be propagated to the ventricles presumably through specialized atrial fibers without depolarizing the atrial muscle.[31,32] This may result in a sinoventricular conduction in the presence of a sinoatrial block. Precise localization of the pacemaker in patients with absence of P waves in the electrocardiogram is usually not possible.[33] When the P waves are absent, an erroneous diagnosis of atrial fibrillation may be made, particularly when the ventricular rhythm is irregular.

The pattern of advanced hyperpotassemia is almost identical to that recorded in dying hearts. Sometimes in advanced hyperpotassemia the S-T segment deviates significantly from the base line and simulates the pattern of acute injury, which may result in an incorrect diagnosis of infarction or pericarditis. Such S-T deviation is probably secondary to the increase in the QRS duration because the injury pattern is rapidly reversible when the QRS duration decreases during treatment of patients with hemodialysis.[34] Both the application of potassium salts on the ventricular surface and the intracoronary injection of potassium salts produce S-T deviation from the base line or a monophasic pattern even when QRS duration is not increased.[35-37] This is due to an injury current arising at the boundary between the myocardium depolarized by potassium and the normal tissue.

An increased concentration of potassium usually depresses the automaticity of an ectopic pacemaker earlier than the automaticity of the S-A node,[38] hence, the antiarrhythmic effect of potassium salts. However, the depression of sinoatrial, atrioventricular, and intraventricular conduction may induce escape beats and rhythms.[33,39] The rate of the escape rhythm is usually slow in adults but may be rapid in children.[40] An increase in plasma K concentration above 12 to 14 mEq./L. causes ventricular asystole or ventricular fibrillation. The latter may or may not be preceded by acceleration of the ventricular rate.[21] Ventricular fibrillation probably results from re-entry which is facilitated by the slow intraventricular conduction and the short duration of the ventricular AP.

The electrocardiographic pattern of hyperpotassemia can be made more normal by increasing the concentrations of plasma calcium and sodium[41-44] and more abnormal by decreasing the concentrations of plasma calcium and possibly also plasma sodium.

Hypopotassemia

A decreased extracellular concentration of potassium increases the RMP of the ventricular fibers and prolongs the duration of the ventricular AP. Fig. 2 demonstrates diagrammatically the relationship between the shape of the ventricular transmembrane AP and the configuration of the ventricular complex in the electrocardiogram. With a decreasing extracellular K concentration the duration of the AP increases.[26] This increase is accompanied by a change in shape: the slope of Phase 2 becomes progressively steeper while the slope of Phase 3 becomes less steep. Thus prolongation of the AP is due to lengthening of Phase 3. With a progressive decrease in extracellular K concentration, the repolarization slope not only becomes slower but also changes progressively in shape from convex to concave (Fig. 2,*D*).[4,8] These changes in the shape of the AP are reflected in the electrocardiogram as a progressive depression of the S-T segment, a decrease in the T wave amplitude, and an increase in the U wave amplitude in the standard limb and

precordial leads. As long as the T wave and the U wave are separated by a notch the duration of the Q-T interval is unchanged.[36,37] In more advanced stages of hypopotassemia the T wave and U wave are fused and an accurate measurement of the Q-T interval is not possible. The voltage of the U wave is usually lowest in Lead aVL, and therefore this lead is useful in recognition of the true duration of the T wave and the Q-T interval. Several methods of differentiating U waves from T waves in doubtful cases have been developed.[37] The elevation of the U wave is most pronounced in the leads which show the highest upright U waves in normal persons, that is in Leads V_2 or V_3. The normally negative U wave in Lead aV[illegible] becomes more negative in the presence of hypopotassemia. As long as the duration of the S-T segment and that of the interval from the onset of QRS to the apex of the T wave (Q-aT) are measurable, they are not prolonged.[37] Since the duration of mechanical systole does not change in hypopotassemia one can best describe the development of the pattern of hypopotassemia as a gradual shift of the major repolarization wave from systole into diastole. In Fig. 2,A the amplitude of the repolarization wave inscribed during systole (T) is significantly greater than the amplitude of the repolarization wave inscribed during diastole (U). In Fig. 2,B both waves are of equal amplitude, whereas in Fig. 2,C and D the amplitude of the repolarization wave inscribed during diastole is greater than that inscribed during systole. It was mentioned earlier that in rabbit hearts perfused with solutions containing a normal concentration of potassium the end of the action potential on the surface of the ventricle coincides approximately with the end of the T wave and the U wave is inscribed after the repolarization is completed (Fig. 2,A). During perfusion with a solution low in potassium the duration of the AP coincides approximately with the duration of the Q-U interval (Fig. 2,B-D). The normal U wave is probably not produced by repolarization of the ventricular fibers but by some other process, such as repolarization of the Purkinje fibers or by stretch potentials engendered by ventricular relaxation.[39] It has been suggested that in hypopotassemia the U wave is superimposed on the gradually increasing diastolic potential produced by the prolonged duration of the ventricular repolarization.[39] If this assumption is correct, then the progressive increase in U wave amplitude in hypopotassemia may be more apparent than real. This concept finds some support in the observations that the intervals from the onset of the QRS complex to the apex and the end of the U wave (Q-aU and Q-U intervals) are not altered during the development and regression of the pattern of hypopotassemia.[37]

A lowering of the extracellular concentration of potassium increases the RMP and the amplitude of the ventricular AP.[4] Such hyperpolarization would not be expected to increase the upstroke velocity of the AP and the conduction in the ventricles, because the upstroke velocity is maximal when the RMP is about −90 mv.[48] On the contrary, hyperpolarization could possibly decrease the conduction velocity by increasing the interval between the RMP and the threshold potential. In the typical pattern of advanced hypopotassemia the amplitude and the duration of the QRS interval are increased. The QRS complex is widened diffusely, which suggests that the intraventricular conduction disturbance is not due to a local block in one of the bundle branches, but to a generalized slowing of conduction in the ventricular myocardium and/or peripheral conducting system (Purkinje fibers). Whether the slowing of intraventricular conduction is actually due to hyperpolarization of the ventricular fibers or to a slower propagation in the incompletely repolarized Purkinje fibers remains uncertain. In adult patients with hypopotassemia the QRS duration is only seldom increased by more than 0.02 second. However, in children the QRS widening may be more pronounced. The amplitude and the duration of the P wave in hypopotassemia is usually increased and the P-R interval is frequently slightly or moderately prolonged.[37,43-44]

The electrocardiographic diagnosis of hypopotassemia is most commonly based on the abnormalities of the S-T segment, T wave and U wave. In an attempt to evaluate quantitatively the pattern of

hypopotassemia we considered the following three electrocardiographic features: (1) depression of the S-T segment of 0.5 mm. or more; (2) U wave amplitude greater than 1 mm.; and (3) U wave amplitude greater than T wave amplitude in the same lead.[8] We analyzed in each of the electrocardiograms one limb lead and one precordial lead, both with the tallest U wave. These two leads could contain a maximum of six features. The electrocardiogram was considered to be "typical" of hypopotassemia if three or more of the described features were present in the two leads, and to be "compatible" with hypopotassemia if two of the described features or one of the features related to the U wave were present. When the plasma K concentration was less than 2.7 mEq./L., the electrocardiograms were "typical" in 78 per cent and "compatible" in 11 per cent of all patients. When the plasma K concentrations ranged between 2.7 and 3.0 mEq./L., the electrocardiograms were "typical" in 35 per cent and "compatible" in 35 per cent of all patients. However, "typical" electrocardiograms were present in only 10 per cent of patients with a plasma K concentration between 3.0 and 3.5 mEq./L. In a more recent study of 107 patients with plasma K concentrations below 3.2 mEq./L., the electrocardiograms were typical or compatible in 78 per cent of the patients.[4] The electrocardiographic changes showed a better correlation with the plasma K concentration than with any of the clinical symptoms.[8] Other workers obtained full agreement of electrocardiographic and laboratory findings in patients whose plasma K concentration was lower than 2.3 mEq./L.[11] or 3.0 mEq./L.[8]

When the electrocardiogram was monitored during the administration of potassium in patients with hypopotassemia, changes in the amplitude of the T wave and U wave reflected fairly accurately the changes in the plasma concentration of potassium.[3] It was observed that the prediction of the change in concentration was more accurate when the amplitudes of the U and T waves were considered together rather than separately.

Recognition of hypopotassemia is frequently difficult in the presence of tachycardia. Since S-T depression and low T wave amplitude commonly occur in patients with tachycardia, the diagnosis of hypopotassemia may require the demonstration of an increased U wave amplitude. However, the U wave amplitude is generally inversely proportional to the duration of the preceding R-R interval,[4] and therefore it is not always appreciably increased even in patients with advanced hypopotassemia. Moreover, in tachycardia the U wave usually merges with the terminal portion of the T wave and with the P wave. The only indication of the presence of the U wave may be a prolonged descent of an apparently normal T wave. In such cases the P wave is usually superimposed on the descending limb of the T wave and on the U wave. When this occurs, the P wave is tilted because its onset is situated farther from the base line than is its end.[9] After the correction of hypopotassemia, the diastolic potential responsible for the uplifting of the P wave decreases and the initial portion of the P wave descends to the base line. Tilting of the P wave is not always associated with an underlying U wave. When the rate is very rapid or when the P-R or Q-T interval is prolonged, the U wave may be superimposed on the descending limb of the T wave.

In left ventricular hypertrophy the amplitude of the U wave is frequently increased even in the absence of hypopotassemia. However, hypopotassemia may be suspected when the S-T segment is depressed in the right precordial leads, because in a pattern of uncomplicated left ventricular hypertrophy the S-T segment in these leads is usually elevated. Digitalis frequently causes S-T and T changes similar to those caused by hypopotassemia, but digitalis does not increase appreciably the amplitude of the U wave. Quinidine increases U wave amplitude, and the electrocardiograms of patients receiving both digitalis and quinidine show a pattern which is indistinguishable from the pattern of hypopotassemia. This pattern may also be present in patients receiving digitalis with other antiarrhythmic drugs which have an action similar to that of quinidine, e.g., procaine amide or diphenylhydantoin. The U wave amplitude is also increased in the presence of bradycardia, particularly

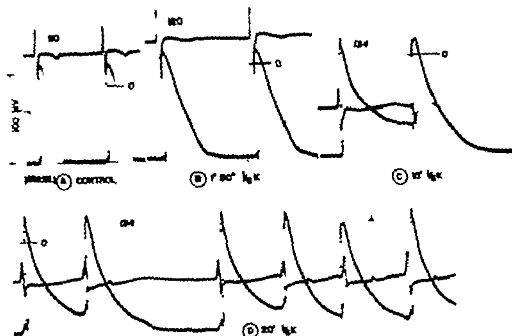


Fig. 3 Changes in the amplitude shape, and duration of the ventricular transmembrane potential during perfusion of isolated rabbit heart with Krebs-Henseleit solution containing 0.8 mEq of potassium per liter The numbers designate the amplitude of the AP in millivolts. 1 D onset of ectopic tachycardia Note that when the repolarization is prolonged the depolarization begins before the fibers are completely repolarized. (From Gettes, L. S Surawicz, B and Shiue J C S. Am J Physiol 203 1135 1962 by permission of the publisher)

in patients with complete A V block and also in some patients with a CVA pattern. However in these patients the T wave amplitude is also frequently increased and the ratio of the T to the U amplitude is usually not altered.

Patients with hypopotassemia not receiving digitalis have atrial and ventricular ectopic beats about three times more frequently than does a control hospital population.[9] The facilitation of ectopic beats is attributed to the prolonged duration of Phase 3 of the AP At the time when the refractory period is over the repolarization is not completed (Fig 3) Thus, the membrane potential is closer to the threshold potential and less current is required for spontaneous depolarization

In isolated preparations a lowering of the concentration of potassium may transform nonpacemaker fibers into pacemaker fibers.[16] Whether this can occur in man is not known We have observed a short coupling interval of the atrial and ventricular ectopic beats in patients with hypopotassemia (Fig 4) which suggests that the effective refractory period of the atrial and ventricular myocardium is short.[13] Systematic studies of the duration of refractoriness in patients with hypopotassemia have not been made. Patients with severe hypopotassemia may show advanced disturbances of intraventricular and atrioventricular conduction ectopic supraventricular tachycardia with block and ventricular tachycardia In isolated hearts perfused with K-deficient solutions the appearance of conduction disturbances and ectopic beats indicates an imminent ventricular fibrillation.[8] Also in man hypopotassemia can produce ventricular fibrillation.[11]

Arrhythmias in patients with hypopotassemia are similar to those produced by digitalis probably because both hypopotassemia and digitalis increase the automaticity of ectopic supraventricular and ventricular pacemakers and prolong atrioventricular conduction. I observed the following arrhythmias in patients with hypo-

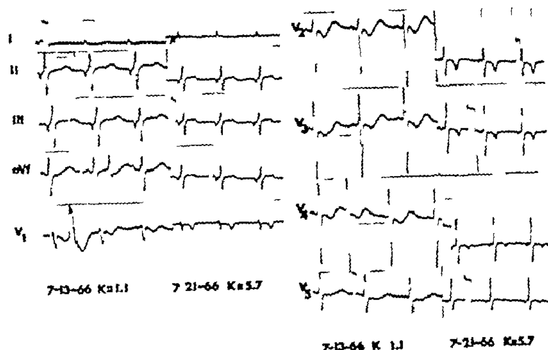


Fig 4 Electrocardiograms of 65-year-old woman with chronic pyelonephritis renal insufficiency and vomiting before and after treatment with potassium salts. Note the typical pattern of hypopotassemia on July 13 1966 and the short coupling interval of the ventricular ectopic beats which interrupt the T waves of the preceding beat. Leads V and V. Plasma concentration of potassium in milliequivalents per liter

potassemia without heart disease or digitalis therapy ectopic atrial tachycardia with block A V dissociation second degree A V block with Wenckebach periods ventricular bigeminal rhythm ventricular tachycardia and fibrillation It has been well established that hypopotassemia and the depletion of potassium may precipitate ectopic rhythms in animals and in man receiving digitalis.[30,35] We found that all patients with a plasma K concentration below 3 2 mEq L who were receiving digitalis had ectopic beats and or A V conduction disturbances.[44]

In isolated rabbit hearts perfused with solutions low in potassium the appearance of A V conduction disturbances ectopic rhythms and ventricular fibrillation could be prevented by lowering the concentration of Ca in the solution [34] However in hypopotassemic patients with hypocalcemia arrhythmias were as common as in hypopotassemic patients without hypocalcemia.[44] Similarly patients with hypopotassemia and acidosis had the same prevalence of arrhythmias as did hypopotassemic patients without acidosis.[44]

Potassium and atrioventricular conduction

This subject deserves a special comment because isolated clinical and experimental observations may appear to be contradictory and be difficult to interpret. Both extremes of high and low concentrations of potassium decrease the A V conduction velocity and increase A V block.[34] The net effect of potassium on A V conduction is determined by the complex interrelationship between the resting membrane potential the threshold potential and the slope of diastolic depolarization in the fibers of the conducting system [34] The most rapid A V conduction in man occurs probably at concentrations of potassium which are somewhat above the upper limits of the normal concentration of potassium However there are marked individual variations. These variations may be caused by various degrees of damage to the conducting system in the diseased heart and by physiologic factors, such as the complex interplay between potassium and acetylcholine.[17,34] Moderate hyperpotassemia may produce shortening of the P R interval

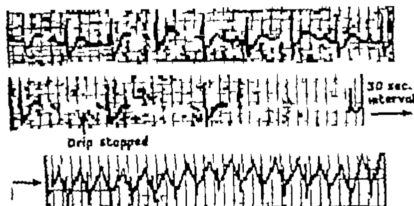


Fig. 5. Lead II of the electrocardiogram of 37 year-old woman with diabetic acidosis treated with insulin, demonstrating high degree of A-V block (interpreted by the author as a complete heart-block) during intravenous administration of KCl solution. See text. (From Sw..., J. D.: Lancet 2:1365, 1964, by permission.)

and occasionally a decreased severity or disappearance of second-degree or third degree A-V block.[*] However, this effect of hyperpotassemia is not uniform; in some patients the A-V block may not be affected whereas in others it may be increased by a small increase in the concentration of potassium.[44] As mentioned earlier, A-V conduction is usually depressed when the plasma K concentration exceeds about 8.0 mEq./L.

A decrease in the plasma K concentration frequently causes disturbances in A-V conduction, although in some patients it appears to improve the A-V conduction. This is probably the basis of therapy with chlorothiazide in patients with incomplete A-V block.[*]

There is an increasing experimental evidence that the effect of rapid changes in extracellular K concentration on the electrophysiologic properties of cardiac fibers is different from the effect of slow changes. Recently, we became aware of a possible clinical significance of the so-called paradoxical phenomenon of Zwaardemaker and Libbrecht (Z.L.). These two investigators noted that, in the perfused frog heart, a change from a K-deficient solution to a solution containing a normal concentration of K results in a transient cardiac arrest or depression of the A-V conduction. We observed the same phenomenon in the isolated perfused rabbit heart and attributed the arrest to the inhibition of diastolic depolarization of the pacemaker fibers by a sudden increase in the concentration of potassium.[*] The resting membrane potential of the atrial and ventricular fibers was not appreciably decreased at the time of inhibition of the pacemaker and there were no atrial and intraventricular conduction disturbances before or after arrest. We were also able to reproduce the same effect in potassium-depleted dogs.[*] It appears that this phenomenon can occur in man with severe depletion of potassium during the administration of potassium salts at a rapid rate. Fig. 5 shows the electrocardiogram of a patient with severe depletion of potassium and plasma K concentration of 1.8 mEq./L. Bradycardia and a high-grade A-V block occurred when potassium was administered at a rate of about 1 mEq. per minute. At the time of A-V block, the electrocardiogram still shows the pattern of hypopotassemia. Subsequently, the rate of administration of potassium was reduced, but after 2 hours the plasma K concentration was 1.4 mEq./L.[*]

Another example of the paradoxical effect of potassium is the decrease in QRS duration observed during the rapid administration of potassium in dogs.[*]

Potassium and excitability threshold

The ventricular excitability threshold of the dog is lowest when the concentration of potassium is slightly elevated, but increases

*See Surawicz and Gettes[*] for references.

sharply when the concentration of potassium exceeds about 7 or 8 mEq./L.[44-47] Although systematic studies of the excitability threshold in man have not been carried out, several clinical observations suggest that, as in the dog, a slight increase in the plasma concentration of potassium lowers the ventricular excitability threshold, and that a further increase raises the threshold. An example of the lowering of the excitability threshold by potassium is its effect on the function of defective pacemakers in which either the stimulus strength is decreased or the tissue resistance around the electrode is increased. A normal response to the pacemaker stimulation can be occasionally restored by the administration of potassium salts by mouth or intravenously.[88] Conversely, the administration of glucose and insulin which lowers the plasma concentration of potassium may cause a decreased responsiveness to the stimulation by a defective pacemaker.[88]

We observed a marked increase in the ventricular excitability threshold in a patient with a transvenous pacemaker when his plasma K concentration was increased to 7.1 mEq./L.[67] One must emphasize that the measurements of excitability threshold in patients with pacemakers do not differentiate between a lack of response to stimulation and the lack of propagation of a local response. However, this is probably of little practical significance since both the excitability threshold and the conduction velocity are probably affected in the same manner. The lowest excitability threshold and the most rapid conduction velocity may correspond to a plasma K concentration of about 6 mEq./L., whereas lower and higher concentrations of potassium decrease the conduction velocity and increase the excitability threshold. It is of interest that ectopic rhythms occurring after myocardial infarction in dogs have been attributed to a moderate increase in the concentration of potassium resulting from a liberation of potassium from the infarcted myocardium. It has been postulated that a lowering of the excitability threshold by moderate hyperpotassemia could make the cardiac pacemaker fibers susceptible to the injury current and thus induce ectopic rhythms.[7]

Effect of potassium on the pre-existing T abnormalities

It has been repeatedly noted that in certain patients moderate increases in the concentration of potassium can change an abnormally low or a negative T wave into an upright T wave. This effect appears to be more pronounced in patients with T wave abnormalities due to myxedema,[71] metabolic disorders, hyperventilation, or orthostatic abnormalities,[72,73] and in patients with anxiety and various psychiatric disorders.[74] Several investigators have administered potassium salts by mouth in order to differentiate the T wave abnormalities produced by structural heart disease from various "functional" abnormalities due to other causes. This procedure may be diagnostically useful because the oral administration of potassium does not alter the angle between the mean spatial QRS and T vectors in persons with a normal QRS-T angle or in patients with myocardial infarction and a pattern of left ventricular hypertrophy.[71] However, in patients in whom the T wave abnormalities were not attributed to heart disease and in patients with T wave abnormalities produced by tilting, the abnormal QRS-T angle became normal after the administration of potassium.[73] If the primary abnormality of the T wave in patients without QRS abnormalities is produced by some form of asynchronous repolarization, e.g., altered duration of the ventricular action potential in certain parts of the myocardium, one must assume that potassium abolishes such nonuniformity more readily in persons with "functional" disturbances of repolarization than in persons with abnormalities of repolarization caused by structural disturbances. The administration of potassium salts in order to differentiate the "functional" T wave abnormalities from abnormalities due to organic heart disease is apparently not a safe procedure since ventricular tachycardia and ventricular fibrillation have been reported to follow such tests.[72,73]

Hypercalcemia and hypocalcemia

Hypercalcemia increases and hypocalcemia decreases the QRS duration but

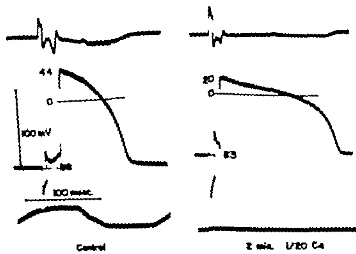


Fig. 6. *From top to bottom:* Electrocardiogram, ventricular AP, and contractile force of isolated rabbit heart before and during perfusion with low-Ca (0.25 mM./L.) Krebs-Henseleit solution. Note the increased duration of the plateau of the AP and the corresponding increase in the duration of the S-T segment. Note the relationship between the end of the T [illegible] and the end of the AP. Recordable contraction is abolished during perfusion with low-Ca solution. (From Dreifus, L. S. and Likoff, W., editors: Mechanisms and Therapy of Cardiac Arrhythmias, New York, 1965, Grune & Stratton, Inc. By permission.)

these changes are usually not pronounced.

Calcium exerts its most prominent effect on the duration of Phase 2 (plateau) of the AP. Perfusion with solutions containing low concentrations of calcium prolongs the duration of Phase 2, whereas the slope of Phase 3 remains relatively unaltered. Prolonged duration of Phase 2 increases the duration of the AP in all fibers. The prolonged atrial AP assumes the shape of the ventricular AP. This, however, does not affect the electrocardiogram because the atrial repolarization potentials cannot be detected in the standard leads. The increased duration of Phase 2 of the ventricular AP results in an increased duration of the S-T segment and of the Q-T interval. This is illustrated in Fig. 6, which also demonstrates that the end of the ventricular action potential coincides approximately with the end of the T wave when the concentration of Ca is normal and low. In patients with hypocalcemia, the S-T segment and the Q-T and the Q-T interval are prolonged, but the Q-T interval seldom exceeds 140 per cent of normal. Therefore, a Q-T that is greater than 140 per cent usually suggests that the U wave is incorporated into the T wave and that the Q-U is being measured.[77] Hypocalcemia can usually be recognized in the electrocardiogram because, with the possible exception of hypothermia, there are no other agents or metabolic abnormalities which prolong the duration of the S-T segment without changing the duration of the T wave. However, measurement of the duration of the S-T segment may be difficult when it is depressed or elevated or when the T wave is diphasic.

The results of correlation between plasma Ca concentration and the Q-T duration are variable.[11,77] We found a good correlation between the duration of the S-T segment and the plasma Ca concentration in patients with hypocalcemia induced by the administration of the calcium binding agent EDTA.[78] In these patients the electrocardiographic pattern was not obscured by the effects of other electrolyte abnormalities or an abnormal blood pH concentration. Since the electrocardiogram is affected by the concentration of the ionized rather than the total calcium, it apparently correlates better with the calcium concentration in the protein-free cerebrovascular fluid than with the Ca concentration in the plasma.[73]

*See Legend for reference.

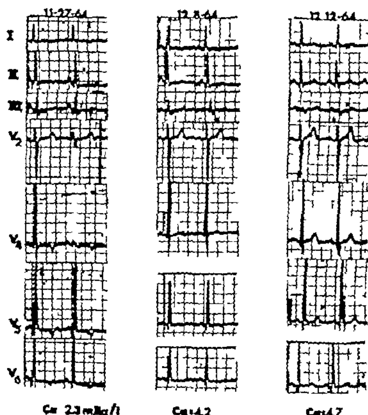


Fig. 7. Electrocardiographic pattern of hypocalcemia simulating myocardial ischemia. Note the pointed inverted T waves in Leads I and V4-6 when the plasma calcium concentration is 2.3 mEq./L. The electrocardiogram becomes normal when hypocalcemia is corrected. This 48-year-old man had hypoparathyroidism but no evidence of heart disease. (Courtesy of Dr. Lee H. Shields and Dr. George Moffitt of Harrisburg, Pa.)

The duration of the T wave in patients with hypocalcemia is not altered, probably because hypocalcemia does not change the slope of Phase 3 of the ventricular AP. However, in patients with severe hypocalcemia the polarity of the T wave may be altered, e.g., the T wave may become flat or inverted in the leads with an upright QRS complex.[11] Such a pattern of hypocalcemia may simulate myocardial ischemia (Fig. 7). In patients with a prolonged Q-T interval due to hypocalcemia, the U wave is usually absent or not recognizable.[9]

In patients with hypocalcemia and hypopotassemia the electrocardiogram shows a prolonged S-T segment and a prominent repolarization wave which consists of T plus U waves. This is due to a prolongation of both Phase 2 and Phase 3 of the AP.[4] When the T wave can be separated from the U wave, the duration of the Q-aT interval is prolonged, whereas the Q-aU and Q-U intervals are normal.[17] Recognition of a pattern of hypopotassemia in the presence of hypocalcemia may be facilitated by the administration of calcium, which shortens the S-T segment and separates the T wave from the U wave.[17] The combination of hypocalcemia and hyperpotassemia which frequently occurs in patients with uremia can be recognized by the presence of a prolonged S-T segment and a narrow, peaked T wave.

An increased extracellular concentration of calcium decreases the duration of Phase 2, so that the ventricular AP acquires the shape of the normal atrial AP. In patients with hypercalcemia the S-T segment is short or absent and the Q-T interval is decreased. However, the U wave amplitude is either normal or increased. In a few in-

stances in which the Q-aU interval was measured its duration was normal

The duration of ventricular ejection is shortened in hypercalcemia and prolonged in hypocalcemia. Therefore the normal relationship between the duration of the Q-T interval and mechanical systole is usually maintained.[72] A high concentration of calcium shortens and a low concentration of calcium prolongs the duration of the effective refractory period. The antiarrhythmic effect of Na_4EDTA has been attributed to a prolongation of the refractory period.[73]

The effect of calcium on various electrophysiologic properties of the heart is dependent on the concentration of potassium. The most important aspects of the complex relationship between calcium and potassium can be summarized as follows. Intraventricular and atrioventricular conduction disturbances and the facilitation of ventricular fibrillation caused by an increased extracellular concentration of potassium can be reversed or prevented by increasing the external concentration of calcium. Conversely, intraventricular and atrioventricular conduction disturbances and the facilitation of ventricular fibrillation caused by a lowering of the extracellular concentration of potassium can be reversed or prevented by decreasing the external concentration of calcium. It must be emphasized, however, that many of the above-mentioned conclusions are based on experiments made in isolated perfused heart preparations in which the concentrations of calcium and potassium were usually lower than those encountered in patients with electrolyte imbalance.

Abnormalities of magnesium concentration

In the absence of hypocalcemia the concentration of magnesium within the range encountered in clinical situations has no significant effect on the ventricular action potential. When calcium is low, the effect of magnesium on the AP and electrocardiogram is more pronounced. In animal experiments, the pattern of hypocalcemia is exaggerated by hypomagnesemia and corrected by hypermagnesemia. This suggests that abnormal concentrations of magnesium may modify the electrocardiographic pattern of hypocalcemia. However, a rapid increase in the plasma concentration of magnesium failed to change the pattern of hypocalcemia (Fig. 8). Therefore it appears to be unlikely that an abnormal plasma concentration of magnesium can be detected in the electrocardiogram. In children with tetany, a lack of Q-T prolongation would favor a deficiency of magnesium rather than calcium.

Abnormalities of sodium concentration

An increased concentration of sodium increases the upstroke velocity of the AP. When the intraventricular conduction velocity is decreased because of the decreased upstroke velocity of the AP, an increased concentration of sodium restores a normal intraventricular conduction. In patients with a wide QRS complex due to hyperpotassemia or quinidine, intravenous injections of sodium chloride or sodium lactate shorten the duration of the QRS complex. Fig. 9 demonstrates the effect of the administration of sodium chloride on the electrocardiogram of a dog with intraventricular conduction disturbance induced by the administration of quinidine. In the absence of intraventricular conduction disturbances due to hyperpotassemia, quinidine, or possibly other causes such as hypoxia, the electrocardiogram is probably not appreciably affected by hypernatremia. I have observed electrocardiographic abnormalities which could possibly be attributed to hypernatremia in only one patient who had an abnormal thirst mechanism attributed to a hypothalamic lesion. Fig. 10 demonstrates that when the concentration of sodium was 216 mEq./L., the T waves were inverted. The electrocardiogram of this patient, who had no evidence of organic heart disease, turned to normal when hypernatremia was corrected by hydration. However, the regression of T wave changes occurred slowly and it remains uncertain whether the T wave abnormalities were due to hypernatremia. A similar electrocardiographic pattern has been produced by the administration of sodium chloride into the coronary artery of the dog[54] and man.[56]

A low concentration of sodium decreases the upstroke velocity and the amplitude

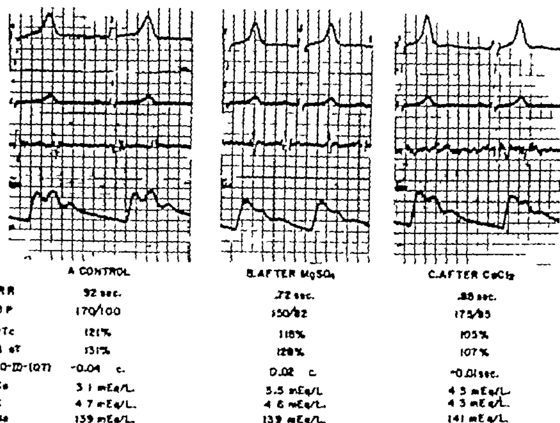


Fig. 9 ... and ... the electrocardiogram, phonocardiogram, and brachial arterial pressure tracing in ... renal insufficiency and hypocalcemia. *A*, Control. *B*, After intravenous administration of $MgSO_4$ ... increased heart rate but no significant change in the duration of Q-T interval. *C*, After ad... $CaCl_2$ shortening of Q-T. Abbreviations: *RR*, R-R interval; *BP*, Blood pressure, mm. Hg; *QTc*, ... duration corrected for rate; *QaT*, Duration of the interval from Q to the apex of the T wave corrected ...; *(Q-II)-(QT)*, Duration of the Q-T interval subtracted from the interval between the onset of the QRS complex and the second heart sound; *Ca*, *K*, and *Na*, Plasma concentrations of calcium, potassium, and sodium, respectively. (From Surawicz, B.: Am. J. Cardiol. 13:636, 1963, by permission of the publisher Reuben H. Donnelley Corp.)

of the AF. However, a decrease in sodium concentration that is compatible with life does not alter the electrophysiologic properties of cardiac fibers appreciably.[44] The effects of hyponatremia cannot be recognized in the electrocardiogram.

Abnormalities of blood pH

Acidosis and alkalosis are usually associated with alterations in the concentration of potassium and ionized calcium which modify the electrocardiographic patterns in the manner outlined above. Whether the modifications of pH per se produce a specific electrocardiographic change is therefore difficult to determine. In patients with hypopotassemia the typical electrocardiographic pattern is found in the presence of both acidosis and alkalosis.[42]

Factors affecting correlation of the electrocardiogram with plasma electrolyte concentrations

The specific effect of electrolytes on the electrocardiogram can be modified by a number of variables. The most important of these are (1) variation in the basic electrocardiographic pattern upon which the abnormalities caused by electrolyte imbalance are superimposed, (2) nonspecific effects due to the changes in the rate or rhythm caused by abnormality of the elec-

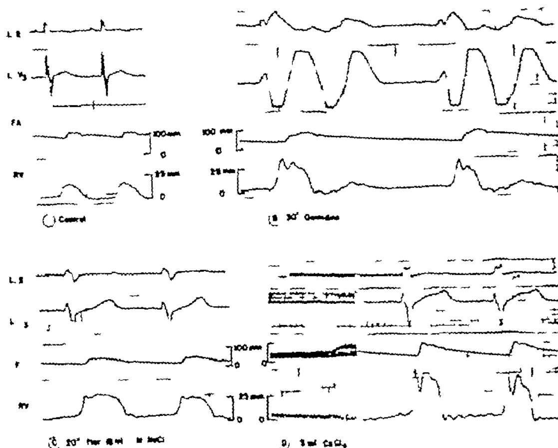


Fig 9 Leads II and V of the electrocardiogr m femoral arterial pressure (FA), and right en ricular pressure (RV) of 20-kilogram dog before (A) and after 30 minutes of intra enou administra ion of q inidine gluconat solution (B). Note the bizarre configuration of the entricular complex in the electrocardiogram, ith ew ide QRS complex. Twenty seconds after the administration of 15 ml of 4 molar sodium chloride the duration of the QRS complex decreases (C). There is slight increase in the QRS interval after he administra ion of calcium chloride (D). (U published observations of A Mazzoleni nd B Sura)

trolyte concentration (3) repolarization changes secondary to intraventricular con duction disturbances caused by the abnormal electrolyte concentration and (4) modifications introduced by the effect of one electrolyte on the concentration and activity of other electrolytes.

The apparent naccuracy of the electrocardiogram in predicting the concentration of electrolytes n the plasma of a patient has been frequently attributed to an assumed effect of intracellular electrolytes on the electrocardiogram The extent to which variations in the intracellular concentrations of electrolytes affect the electrocardiogram is difficult to determine Studies of isolated hearts perfused with solutions containing low and high concentrations of potassium suggest that the electrocardiogram reflects alteration n the transmem brane action potential produced by the altered potassium gradient c ss the mem brane However n th acute exper ments the changes in th grad ent a e due largely to changes in the extracellula concentra tion of potassium

Numerous linical nd experimental observations demonst t that all patterns of electrolyt mbal nc an be produced or corrected b rapidly alter ng the extr cellular con entration of electrolytes The rapidity of the changes ules against an ppreciable change in the int acellular concentration of these ions A good exam

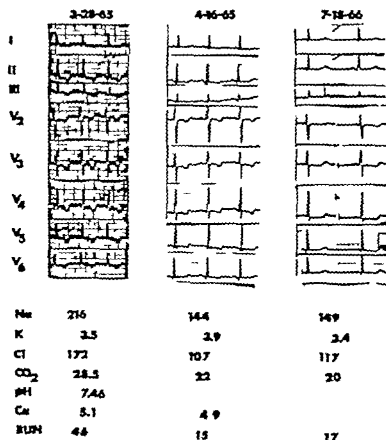


Fig. 10 Electrocardiogram of 25-year-old man with hypernatremia which was attributed to suppressed thirst secondary to an assumed hypothalamic lesion. The abnormalities of plasma electrolyte concentrations and the elevation of blood urea nitrogen concentration (BUN) were readily corrected by forcing the patient to drink water. Note the inverted T waves in all leads when the plasma concentration of Na is 216 mEq./L. on March 28 1965. On April 16 1965 plasma electrolyte concentration and BUN were within normal range and the T waves are less deeply inverted. On July 18 1966, the T waves are upright. Slight depression of the S-T segment in Leads V[illegible] is attributed to slight hypopotassemia. See text.

ple of this is the patient with familial periodic paralysis or the patient treated for diabetic acidosis in whom the electrocardiographic changes parallel the rapidly changing levels of plasma K concentration. Relatively small changes in the extracellular concentration of potassium have large effects on the transmembrane K gradient. A decrease in plasma K concentration from 4.0 to 2.0 mEq./L. changes the ratio of intracellular to extracellular K from 30:1 to 60:1. Conversely, when the plasma K concentration is 8.0 mEq./L., the ratio of intracellular to extracellular K becomes 15:1. It appears to be unlikely that in living myocardial fibers changes in intracellular potassium alone can contribute to changes of similar magnitude in the transmembrane gradient. The intracellular concentration of potassium in the myocardium is relatively stable under various experimental conditions. In cats and rats subjected to experimental procedures that alter total body electrolyte content, the myocardial concentration of potassium changed less than 15 per cent, whereas changes in the skeletal muscle content were greater.[17, 9] In hearts perfused with low, normal, and high concentrations of potassium, the intracellular concentration of potassium was not significantly different.[12] If these results in animal experiments are applicable to man, one must conclude that the alterations of potassium gradient

across the myocardial cell membrane are largely determined by alterations in the extracellular concentration of potassium

The electrocardiogram does not reflect the changes in total body potassium unless the plasma K concentration is altered Patients with large deficits of total body potassium had normal electrocardiograms so long as their plasma K concentration was normal In dogs, the electrocardiographic patterns of hypopotassemia were identical when the plasma K concentration was reduced by hemodialysis and by the administration of insulin with glucose.[*] In the first procedure potassium was removed from the cells and the total body potassium was decreased whereas in the second procedure the total body potassium remained unchanged

The variability of criteria employed in the evaluation of the electrocardiogram the wide range of normal electrolyte concentrations, and the multitude of other factors mentioned above are more than sufficient to account for the difficulties encountered by the electrocardiographer when he attempts to predict concentrations of plasma potassium and plasma calcium from the electrocardiogram particularly when these concentrations are only slightly outside the normal range. This does not diminish the significant role of the electrocardiogram in the detection of cardiotoxic effects produced by electrolyte abnormalities.

The accuracy of the electrocardiographic diagnosis improves when the interpreter is alert to the possibility of an electrolyte imbalance, when control tracings are available for comparison and when the patient is followed with serial tracings. Monitoring of the electrocardiogram during the intravenous administration of potassium and calcium salts or of agents lowering the concentrations of these ions contributes significantly to the effectiveness and safety of such therapy

Conclusions

In the past 10 to 15 years progress has been made in the understanding of the effects of ions on the cardiac transmembrane action potentials. Changes in the resting membrane potential and the shape and duration of the action potential explain the electrocardiographic pattern of electrolyte imbalance and the electrolyte effects on cardiac rhythm and conduction

The electrocardiogram is a fairly sensitive indicator of changes [illegible] plasma concentrations of potassium and calcium and is useful in the recognition of these changes. Abnormal concentrations of sodium magnesium and hydrogen ions are seldom recognizable in the electrocardiogram

[*] For references, see Surawicz and Lepeschkin[6] and Surawicz et al.

REFERENCES

1 Thomas, R. M Mylon, E and Winternitz, M C. Myocardial lesions resulting from dietary deficiency Yale J Biol & Med. 12:345 1940.
2. Molnar Z., Larsen, K., and Spargo, B. Cardiac changes in potassium depleted rats. Arch. Path. 74:339 1962
3. Heggtveit, H. A. The cardiomyopathy of magnesium-deficiency [illegible] Bajusz, E., editor Electrolytes and cardiovascular diseases, New York, 1965 S. Karger p. 204
4 Hoffman, B. F and Cranefield, P F Electrophysiology of the heart New York 1960, McGraw Hill Book Company Inc.
5 Weidmann, S Elektrophysiologie der Herzmuskelfaser Bern, 1960, Huber
6. Surawicz, B., Lepeschkin, E. Herrlich, H., and Hoffman, B F Effect of potassium and calcium deficiency on monophasic action potential electrocardiogram and contractility of isolated rabbit hearts, Am J Physiol. 196 1302 1958.
7 Surawicz B Lepeschkin, E and Herrlich, H C. Low and high magnesium concentrations at various calcium levels effect on the monophasic action potential, electrocardiogram, and contractility of isolated rabbit hearts, Circulation Res. 9:811 1961
8. Gettes, L S., Surawicz, B and Shiue, J C S. Effect of high K, low K and quinidine on QRS duration and ventricular action potential, Am J Physiol. 203 1135 1962
9 Surawicz, B Electrolytes and the electrocardiogram, Am J Cardiol 12:656, 1963. ✓
10. Weidmann, S Shortening of cardiac action potential due to brief injection of KCl following the onset of activity J Physiol 132 157 1956
11 Winkler A W Hoff H E and Smith, P K Electrocardiographic changes and concentrations of potassium [illegible] serum following intravenous injection of potassium chloride, Am J Physiol. 124:478, 1938
12. Levine H D Vazifdar J P Lown, B and Merrill, J P "Tent-shaped" T waves of normal amplitude in potassium intoxication, Am Heart J 43:437 1952.
13 Dutcher W A Walkin, K G., Essex, H F Pruitt, R. D and Burchell H. B The effect of changes in concentration of cations on the

lect ocardiogram of the isolated perfused heart Am Heart J 43:801 1952
14 Braun, H A Surawicz, B and Bellet S T w res E h perpotassemia Am J M Sc 230 147 1955
15 Dreifus, L S and Pick, A A cli ical orrela tive study of the electrocardiogram in lectro-l lyte imbalance, Circulation 14:815 1956
16 Levine, H D Merrill, J P and Sommerville, W Advanced disturbances of cardiac mechanism in potassium intoxication in man, Circulation 3:889 1951
17 Herndon, R Meroney W nd Pearson C The electrocardiographic effect of alter tion in oncentration of plasma chemicals, Am. Heart J 50 188 1955
18. Lepeschkin E Surawicz, B nd Herrlich H C Differences in the effect of lectrolytes on the trial and ventricular action potential of isolated perfused rabbit hearts, Fed. Proc. 19 112 1960
19 Surawicz B and Gettes, L S Tw types of cardiac arrest produced b potassi m Circulation Res 12:415 1963
20 DeM llo, W C nd Hoffma B F Potassium ions and lectrical activity of specialized cardiac fibers, Am J Ph siol 199 1125 1960.
21 Hoffman, B F The pathoph siology of failure of impulse transmission t the ventricle, in Sur wic B and Pellegrino, E. ed tors Sudden ardiac death New York, 1964 Gr ne & Stratt n, Inc p 86
22 Vassalle M nd Hoffman, B F The spread of sinus activ tion during potassi m administration Cir ulation Res 17:285 1965
23 Vassalle M Greenspan K Jomain, S., and Hoffman B F Effects of potassium on a tomatic ty and onduction of canine hearts, Am J Phy iol 207:334 1964
24 Levine H D Wanzer S H and Merrill, J P Dial zable current of injury in potassium intoxication resembling acut myocardial infarction of peric arditis, Circulation 13:29 1956.
25 Wolferth C C Bellet S. Livezey M M nd Murph F D Negati displacement of the RS-T segment in the electrocardiogram and its relationsh ps to pos tiv deplacement an experimental stud Am Heart J 29:220, 1945
26. Soloff L de los Sa tos, G A nd Oppenheimer J M Elect ocardiographic changes produced by potassium and other ions injected into the coronary arteries of intact dogs Circulation Res. 8:479 1960
27 Krotkiewski, A and Surawicz, B. Effect of intracoronary K infusion on myocardial contractil ty nd epicardial lectrocardiogram Circulation (Suppl. III) 34 150 1966.
28. Antoni, H Herkel, K nd Flecken tei A. Die Restitution der automatischen Erregungsbildung in Kalium-gelahmten Schrittmacher Geweben durch Adrenalin, Pflugers Arch. 277:633 1963.
29 Fisch, C., Feigenbaum H nd Bowers, J A. Nonparoxysmal A V nodal tachycardia due to potassium Am J Cardiol 14:357 1964
30. Pick, A Arrhythmias and potassium in man, Am. H art J 2:295 1966.
31 Surawicz, B Method of production of ventricular fibrillation Surawicz and Pellegrino, p. 64
32 Lepeschkin, E. The ole of electrolytes and metabolic influences on the lectrocardiogram, Advances in Cardiology 2 189 1959
33 Mueller P Da Elektrokardiogramm bei Elektrol tstorungen, Sch eiz Med Wchnschr 92:842, 1962.
34 Garcia-Palmieri, M R Reversal of hyperkalemic cardiotoxicity with hypertonic saline, Am. Heart J 64:483 1962
35 Hecht, H Heath J Maier E. S., Lange R and Nelson, C V The cellular basis for the lectrocardiographic changes ssociated with alterations in serum potassium J Clin. Invest 36:897 1957
36. McAllen P M The electrocardiogram ssociated with low levels of serum potass um Brit. Heart J 13 159 1951
37 Surawicz, B nd Lepeschki E Elect ocardiographic pattern of hypopotassemia with nd w thout hypocalcemia, Circulation 8:801 1953
38 Dudel J and Trautw in, W Das Aktionspotential und Mechanogram des Herzmuskels unter dem Einfluss der Dehn ng Cardiologia 25:344 1954
39 Sjostrand T Electrocardiogram in hypopotassemia, Acta Med. Scandina 181 73 1955
40. Weidman S The effect of cardiac membrane potential on the rapid availability of the sodium-carrying system, J Physiol 127:213 1955
41 Cherry J C and Sur wicz, B U usual effects of potassium deficiency on the heart of a child with cystinosis, Pediatrics 30:414 1962.
42 Henderson C B. Potassium nd cardiographic changes in diabetic acidosis, Brit. Heart J 15:87 1953.
43. Surawicz, B Bra n, A. H Crum W B Wagner S. Bellet S and Kemp, R L Quantitative analysis of the electrocardiographic pattern of hypopotassemia, Circulation 16 750, 1957
44. Weaver W F nd Burchell, H B Serum potassium and electrocardiogram in hypokalemia, Circulation 21:505 1960.
45 Davidson S and Surawicz, B Incidence of supraventricular and ventricular ectopic beats and rhythms and of trioventricular conduction disturbances in patients with hypopotassemia, Circulation (S ppl. III) 34:85 1966
46. Surawicz, B Braw A. H Kemp, R. L., Crum W B W gner S. and B llet S. Clinical manifestations of hypopotassemia Am. J M Sc. 233:603 1957
47 Bickel, G Plattner H nd Fabre J Les repercussions cardiaques des alterations du metabolisme du potassi m, Arch. Mal. Coeur 47:203 1954
48. Kunin, A. S., Surawicz B nd Sımms, F A. H Decrease in serum potassium concentrations nd ppearanc of cardiac arrhythmia during infusion of potassium ith glucose in pot sium depleted patients, New England J Med. 266:228, 1962.
49 Sura icz, B nd Lepeschkin, F Effect of

hypopotassemia and certain other factor on the amplitude of the U wave in the electrocardiogram. Circulation 14 1007 1956
50. Surawicz, B. Role of electrolytes in etiology and management of cardiac arrhythmias, Prog Cardiovas. Dis 8:364 1966
51. Gettes, L. S. Surawicz, B. and Kim K. H. Roll of myocardial K and Ca in initiation and inhibition of ventricular fibrillation Am. J Physiol. 211:699 1966
52. Lown, B. Weller J. M., Wyatt, N. Hoigne, R., and Merrill, J. P. Effects of alterations of body potassium on digitalis toxicity J. Clin. Invest. 31:648, 1952.
53. Lown, B. and Levine, S. A. Current concepts in digitalis therapy Boston, 1954 Little Brown & Company
54. Grumbach L., Howard J. W. and Merrill, V. I. Factors related to the initiation of ventricular fibrillation in the isolated heart. Effect of calcium and potassium, Circulation Res 2:452, 1954
55. Paes de Carvalho, A. and Langan, W. B. Influence of extracellular potassium levels on triventricular transmission, Am. J. Physiol. 205:375 1963.
56. Surawicz, B., and Gettes L. S. Effect of electrolytes on the action potential, Dreifus, L.S., and Likoff W. editors Mechanisms and therapy of cardiac arrhythmias. New York, 1965 Grune & Stratton, Inc
57. Feigenbaum, H. Wunsch, C. M. and Fisch, C. Interrelationship of potassium and the vagal action on the sinoatrial pacemaker and on trioventricular conduction, J. Clin. Invest. 44:399 1965
58. Greenspan, K. Wunsch, C. and Fisch, C. The relationship between potassium and vagal action on atrioventricular transmission Circulation Res. 17:39 1965
59. Fisch C. Knoebel, S. B. Feigenbaum H. and Greenspan, K. Potassium and the monophasic action potential, electrocardiogram conduction and arrhythmias, Prog Cardiovas. Dis. 8:387 1966
60. Bettinger J. C., Surawicz, B. Bryfogle, J. W. Anderson, B. H. and Bellet, S. Effect of intravenous administration of potassium chloride on ectopic beats and A-V conduction disturbances, Am. J. Med. 21:521 1956
61. Tobian, L. Prevention of Stokes-Adams seizures with chlorothiazide New England J. Med. 265:623, 1961
62. Surawicz, B. Chlebus, H. and Mazzoleni, A. Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K, Am. H. Heart J. 73:647 1967
63. Swales, J. D. Hypokalemia and the electrocardiogram, Lancet 2 1365 1961.
64. Mendez C., Erlij D. and Moe C. K. Indirect action of epinephrine on intraventricular conduction time Circulation Res. 14 318, 1964
65. Siebens, A. A. Hoffman, B. F. Enson, Y. Farrell, J. F. and Brooks, C. M. Effect of l-epinephrine and l-norepinephrine on cardiac excitability Am. J. Physiol. 175 1 1953.
66. Han, J. Garcia de Jalon, P. and Moe, G. K. Adrenergic effects on ventricular vulnerability Circulation Res 14:516, 1952.
67. Surawicz, B. Chlebus, H. Reeves, J. T. and Gettes, L. S. Increase of ventricular excitability threshold by hyperpotassemia. Possible cause of internal pacemaker failure, J.A.M.A. 191 1049 1965.
68. Walker W. J. Elkins, J. T. and Wood, L. W. Effect of potassium in restoring myocardial response to subthreshold cardiac pacemaker New England J. Med. 271:597 1964
69. Harris, A. S. Bisteni, A., Russell, R. A. Brigham, J. C., and Firestone, J. E. Excitatory factors in ventricular tachycardia resulting from myocardial ischemia potassium major excitant, Science 119:200 1954
70. Harris, A. S. Potassium and experimental coronary occlusion, Am. Heart J. 71 797 1966
71. Sharpey Schafer E. P. Potassium effects on the electrocardiogram of thyroid deficiency Brit. Heart J. 5:85 1943
72. Wasserburger R. H. and Corliss, R. J. Value of oral potassium salts in differentiation of functional and organic T wave changes Am. J Cardiol. 10:673 1962
73. Dodge, H. T. Grant R. P. and Seavey P. W. The effect of induced hyperkalemia on the normal and abnormal electrocardiogram, Am Heart J 45 725 1953
74. Wendkos, M. H. The effects of potassium mixture on abnormal cardiac repolarization in hospitalized psychiatric patients, Am. J. M. Sc. 249 76, 1965
75. Lepeschkin E. Modern electrocardiography Vol I Baltimore 1951 Williams & Wilkins Company
76. Hoffman, B. F. and Suckling, E. E. Effect of several cations on transmembrane potentials of cardiac muscle, Am. J. Physiol. 186:317 1956
77. Yu, P. N. G. Electrocardiographic changes associated with hypocalcemia and hypercalcemia, Am. J. M. Sc. 224:413 1952
78. Surawicz, B. MacDonald, M. G. Kaljot, V. and Bettinger J. C. Treatment of cardiac arrhythmias with salts of ethylenediamine tetraacetic acid (EDTA) Am. Heart J. 58:493 1959
79. Ljung O. The electrocardiogram in hypocalcemia, with special reference to the T wave, Acta Med. Scandinav. 136:56 1949
80. Reynolds T. B. Martin H. M. and Homann, R. E. Serum electrolytes and the electrocardiogram. Am. Heart J. 42:671 1951
81. Bellet, S. and Finkelstein D. Significance of Q-T prolongation in the electrocardiogram Am. J. M. Sc. 222:263 1951
82. Surawicz, B. Effect of Ca on duration of Q-T interval and ventricular systole in dog Am. J Physiol. 205 785 1963
83. Gorman, N. A. West, J. W. and Bellet S. Reversal of the currents of injury by intracoronary injections of calcium chloride. Circulation 16:889 1957
84. Krakauer, A. Lepic J. and Surawicz, B. Unpublished observations.

85. Smith, R F Harthorne J W and Sanders, C. A Vectorcardiogr phic hanges during selectiv coronary artery injection Circulation (Suppl III) 34:218 1966.
86 Trautwei W Generation nd conduction of impulses in the heart as affected by drugs, Pharmacol Rev 15:277 1963
87 Robertson, W va B and Dunihue, F W W ter and electrolyte distrib tion in cardiac muscle, Am J Physiol 177:292, 1954
88. St. George S. Freed S. C., Rosenman, R., and Winderman, S. I fluence of potassium de privation and adrenalectomy on potassium on centration of the myocardium Am. J Physiol. 181:550, 1955.
89 Surawicz, B Kunin, A. S. and Sims, F A. H.: The effects of hemodialysis and glucose-insulin admi istration on plasma pota sium and the electrocardiogram Circulation Res. 12:145 1963

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Reappraisal of digitalis
Part X. Treatment of digitalis toxicity

Alan F. Lyon, M.D.
Arthur C. DeGraff, M.D.
New York, N. Y.

At present, no specific antidote for digitalis counteracts all of the physiologic effects of digitalis without introducing effects of its own. When active treatment of digitalis intoxication is necessary, drugs which counteract one or another of the actions of digitalis must be used, and the choice of an agent is dependent on the particular manifestation of digitalis poisoning which is most hazardous to the patient.

The safest and most consistent method of treatment is withdrawal of digitalis as soon as toxicity is detected. This is always in order when the manifestations are limited to the gastrointestinal tract or central nervous system, or when there are occasional premature contractions or prolongation of the P-R interval or dissociations at normal rates. Restoration of normal function can be expected within hours to days, depending on the glycoside used. Digitalis should be completely withdrawn rather than reduced in dosage. It is reasonable to assume that adequate tissue saturation will remain until after the last toxic sign disappears. At that time digitalis may be administered in a dose lower than that previously used.

An exception is when digitalis toxicity occurs at an exceptionally low dose because of associated hypokelemia. Digitalis must also be withdrawn, and although the toxicity regresses, the body potassium should be repleted, and only then should digitalis be reinstituted. In this case digitalis can be given at the previously effective dose.

More urgent treatment is necessary when toxicity results with arrhythmias that interfere with the function of the heart. These fall into two categories: tachycardia and slow heart rate due to sinus bradycardia or heart block. The drugs available for treatment are not effective in the presence of heart block. The administration of potassium salts in this situation may worsen the block or slow the ventricular rate because of the direct depressant effect of potassium. Isoproterenol, which is sometimes quite effective in improving cardiac rate in heart block of other cause, is likely to produce severe arrhythmias in the presence of digitalis toxicity and should not be used. The treatment of choice for heart block or marked sinus bradycardia due to digitalis is the temporary installation of an endocardial catheter pacemaker and control of the heart rate by electrical stimulation.

The treatment of toxic arrhythmias manifested by rapid heart rate is much less satisfactory. Since the cause of many of these tachycardias may be related to changes in the cell membrane with an alteration in entry of potassium into the cell, the most specific treatment is the

Received for publication Feb. 23, [illegible]
*Chief, Cardiology Section, Veterans Administration Hospital, Bronx, N. Y.
**Professor of Therapeutics, New York University School of Medicine, and Consultant in Cardiology, Bronx Veterans Administration Hospital, Bronx, N. Y.

administration of potassium either intravenously or orally in order to produce slight hyperkalemia and to drive potassium into the cells. This has proved to be most effective in the control of atrial tachycardia with block. Unfortunately, it is inconsistently effective with other rhythms and valuable time may be lost during such treatment for severe arrhythmias such as ventricular tachycardia. Potassium chloride can be used intravenously in life threatening situations in doses of 20 to 40 mEq given over a period of 1 to 2 hours. It can be given orally in less pressing situations as an initial dose of 4 Gm. of potassium chloride in solution followed by 2 Gm. every 4 hours until the arrhythmia is controlled.

The chelating compounds disodium ethylenediamine tetraacetate (EDTA) or sodium citrate reduce the concentrations of ionized calcium in the blood. How this affects digitalis toxicity is not clear, but it is possible that a reduction in serum calcium makes more carrier sites available for the entry of potassium. These drugs are given intravenously. The recommended dose of EDTA is 50 mg. per kilogram given in a 1 per cent solution in 5 per cent dextrose over a period of 20 to 30 minutes. The ideal dosage of sodium citrate, given either in a single injection or as a slow drip, is not clearly established. Both of these agents, when effective, terminate the tachycardias promptly, but they often recur a few minutes later. The recurrent use of EDTA is often accompanied by malaise, nausea, vomiting, urinary urgency and frequency, tetany, and hypotension. The use of EDTA in high dosage may also cause thrombophlebitis and damage to proximal renal tubules. The use of large amounts of citrate as sodium citrate might cause or increase heart failure. The action of these drugs is not only brief but inconsistent. One author reported that sodium EDTA was only 50 per cent effective with atrial tachycardias and ventricular premature contractions, although somewhat more effective with ventricular tachycardia. It is interesting that these drugs can consistently abolish the electrocardiographic pattern of digitalis effect. It has been suggested that EDTA may be particularly useful in ventricular tachycardia in the presence of complete block because it can increase conduction in the A-V node, but there is little clinical documentation of its effectiveness in that situation.

Another agent with a somewhat similar mode of action is diphenylhydantoin. This drug probably acts by reducing intracellular sodium and increasing intracellular potassium. It is given as an initial dose of 6 mg. per kilogram intramuscularly; 30 minutes later 1 mg. per kilogram can be given intravenously and repeated every 10 to 15 minutes if necessary. Clinical studies on its effectiveness in digitalis intoxication are few, but some successes are reported. Its major hazard is pacemaker depression.

Ryanodine, a natural alkaloid insecticide, has been studied by several investigators. Although it can stop digitalis arrhythmias, it usually produces new arrhythmias and has a marked negative inotropic effect at therapeutic levels. It is not approved for general use.

The standard modalities for treating tachycardias not due to digitalis are cardiac depressant drugs such as quinidine and procainamide, digitalis, and synchronized precordial shock. Digitalis is, of course, inappropriate when the tachycardia is produced by digitalis. The others are all effective to some degree in digitalis toxicity, but all are associated with increased hazard in this situation. The greatest hazard is probably attached to synchronized countershock. Although cases of prompt and permanent remission of digitalis-induced tachycardia without side effect from the shock have been reported, it has also been shown that shock is less likely to revert tachycardia due to digitalis than tachycardia due to other causes, and that the tachycardia is more likely to recur rapidly. The incidence of shock toxicity, particularly ventricular fibrillation, is also greatly increased. It is now generally considered that synchronized precordial shock is contraindicated in digitalis toxicity.

The use of another electrical treatment, paired pulse stimulation, has had little clinical trial and remains as an interesting laboratory phenomenon. In this technique a catheter in the heart paces the heart faster than the tachycardia and takes control of the rhythm. The stimuli are ingeminal and the second is so close to the first

that no contraction occurs and the effective rate is halved At present this is still an experimental laboratory procedure

Quinidine or procainamide will be effective in most ventricular tachycardias, but in the presence of digitalis intoxication there is a higher incidence of ventricular fibrillation than would otherwise be expected Nonetheless as of this writing they remain the drugs of choice for life-threatening tachycardias due to digitalis in which the effect of potassium is considered to be too slow and unpredictable. Intravenous procainamide in doses of 100 mg per minute until the tachycardia terminates, hypotension or new arrhythmias occur or a dose of 2 Gm is reached is the most widely accepted routine.

Propranolol a beta adrenergic blocking agent is now undergoing intensive study in the treatment of digitalis intoxication. Preliminary reports suggest that this agent is very effective in the control of arrhythmias due to digitalis. It has a direct blocking effect on the A V node and can slow the ventricular rate when digitalis produces atrial fibrillation with a rapid ventricular rate. Its negative inotropic effect may however worsen incipient or existing congestive heart failure. Further clinical study is necessary but it seems to be possible that this drug may be the best treatment available for tachycardias due to digitalis.

REFERENCES

1 Szekely P and Wynne N A. Effects of calcium chelation on digitalis-induced cardiac arrhythmias, Brit Heart J 25:589 1963
2. Taylor R. R., Johnston, C I and Jose, A D Reversal of digitalis intoxication by beta-adrenergic blockade with pronethalol, New England J Med 271:877 1964.
3 Frommer P L Robinson, B. F and Braunwald E. Studies on digitalis. XII The effects of paired electrical stimulation on digitalis-induced arrhythmias, J Pharmacol. & Exper Therap 151 1 1966.
4. Kahn M Shiffman, I Kuhn, L. A., et al Effects of Ryanodine in normal dogs and in those with digitalis-induced arrhythmias Hemodynamic and electrocardiographic studies, Am. J Cardiol. 14:658 1964
5. Lang, T W Bernstein H., Barbieri, F F Gold, H. and Corday E Digitalis toxicity Arch. Int. Med. 116:573 1965
6. Corday E., and Skelton R. B. T The use of citrate salts for testing digitalis-induced cardiac arrhythmias in the experimental animal, Am. Heart J 67:237 1964

Annotations

Determination of glomerular filtration rate with ^{57}Co-B$_{12}$ measurement of protein binding

I ulin ha long been ac epted as the standard of reference for the measurement of glomerular filtra tion rat (GFR However the hemical determination of this subst nce is laborious process. This has led t the se rch for simple yet reliable method of measuring this pa meter The endogenous reatinine clearance is widel used nd i probably satisfactory during short observations in normal ma U fortunatel creatinine is excreted by tubular secretion in ma y species including man The endogenous creatinine learance is unreliable in patient th renal dise se, and particularly in those ith nephrotic yndrome

The use of radioactive tami B for the mea surement of GFR began w th the work of Nelp, W gner nd Rela They showed that cyanocobalamin is excreted the urine by glomerular infilt tion A ph siologic levels, the itamin in lasma is lmost ompletel bound to protein and not ex pe filtr tion But Smith has pointed out t ndard of reference for the measurement of glomerular lear nc must be ompletely filter ble t the glomerul Nelp and co orker over came this major diffi ulty by giving large dose of unlabeled tamin t saturat the protein-binding sites before injecting the adioact tamin, nd by including imilar dose the susta ning infusion administered throughout the learance periods. They used eq il brium dialysi t measure the binding of the labeled tami to plasma proteins. Using the freely dialyzable plasma radioacti ity to calculate the urine/plasma (U P) ratio for ^{57}Co-cy nocobalamin they found good agreement with the simultaneously measured in lin clearance They stressed the relat e simplicity and the accuracy of measuring GFR in this y

Cutler and Glatte[4] confirmed these observations. They noted, however that binding might vary between patients, and in the same patient on dif ferent occasions. Subsequentl two report were published in which the total plasma radioactivity uncorrected for protein binding wa used to ku- late the U/P r tio for cyanocobalamin. One group claimed a close correspondence ith the imul taneou inul learance. The other[4] found con siderable d erence

Foley Jones and Clapham re-examined this problem. To a oid a y uncertai ties in pre-satura tion, they used the technique tandardized by Nelp and by C tler and Glatte which as show to raise the serum B level five-hundred to one-thousand fold. They found that the use of dialyzable plasma radioactivity ga e a much closer correspondence bet een the B$_{12}$ clearance and the simul taneous inulin clearance tha did the use of total plasma activity

I their series, the mean U/P ratio for cyanocobalamin, ncorrected for binding was significantly less than the U/I ratio for in lin when correction was made for protein binding, this difference disappe red (Figs. 1 nd 2)

The protein binding of Co-cyanocobalamin was measured by counting the plasma samples before nd after dialysis for 24 hours at room tem perature gainst 4 liters of physiologic saline. An analysis of ariance performed on the result of their measurements of binding showed clearly that the percentage bound aried considerably bet een subjects. The ariation between subjects far ex ceeded the variation found in y one subject during one set of clearance measurements.

T ble I summarizes the results of the published comparisons of plasma total B$_{12}$ clearance with sim ltaneous inulin learance. It can be seen that failure t correct for protei binding may lead to an ppreciable and variable underestimate of GI R. For these reasons, both theoretical and practical, the measurement of protein binding cannot be omitted i accurat work.

Attempt re now being made to develop

Table I

Authors	Clearance of ^{57}Co-B$_{12}$† / Clearance of inulin
Nelp et al. (1964)	90%
C tler nd Glatt (1965)	85%
Breckenridge and Metcalfe-Gibson (1965)	99%
M lamos et al. (1966)	74%
Foley et l. (1966)	83%

*Calculated from data given by he uthors.
†Uncorrected for protein binding.

Table II

	Time (min)						
	25	*33*	*52*	*62*	*124*	*235*	*329*
^{58}Co-B_{12} plasma activity Percentage bound	25 6	32 7	34 2	32 7	42 9	44 0	52 3

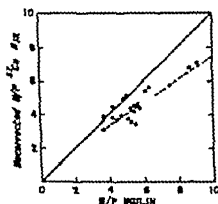


Fig. 1 Relationship bet een U/P ^{57}Co-cyanocobalamin uncorrected for protein binding and U/P Inulin. The continuous line represents 1:1 relationship. The calculated regression equation was y = 0 7 + 0.7x (= 0.86).

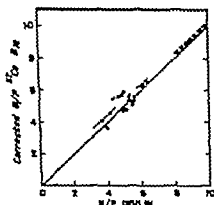


Fig. 2 Rela ionship bet een U/P ^{57}Co-cyanocobalamin, corrected for protein binding nd U/P Inulin. The calculated regression equation as y = 0 36 + 0 97 (= 0 94).

method of measuring protein binding thout the delay i ol ed in 24-hour dialysis. The use of activ ted charcoal to adsorb the free B has been suggested[20,21] However charcoal is capable of adsorbing B -binding protein as ell as free B [22,23] Gottlieb nd associates[24] found that charcoal pre treated with albumin or dextran no longer adm ts protein molecules, so that only free cyanocobalamin is now adsorbed. Preliminary studies in this depart ment indicat good agreement bet een est mates of binding obtained by dialysis and those obtained by the use of coated charcoal. The use of pretreated charcoal may offer an accurate and rapid substit te for dialysis in clearance ork.

A quite different pproach to the use of Co-B for the measurement of GFR was proposed by Slapak and Hume. They used the rat of disappearance of radioacti e B from the plasma after a single injection to calculate the GFR. This method depended on the linearity of the disappearance curv when replotted on semilog paper nd on the assumption that this disappearance conforms to single exponential f nction. Airell suggested that the disappearan curv as better fitted by t exponential functions wi h sharp inflexion be tween them nd used the second function to alculat GFR

However the mathematical analysis used by Slapak and Hume was heoreticall nsound[25] and our observ tions suggest that the disappearance of plasma ac h y af er single injection does not conform either to single exponential or to tw exponential functions. It seems t be mor likely that mul icompartment system is in olved The issue is further complicated by the fact tha as the plasma activity declines, the per entage bound rises progressi el as Table II show

It seems, therefore, tha grea deal more ork needs be done befor single-injection technique ca be validated.

F om this review it is pparent that onstant infusion technique is needed to estimate the renal clearance of ^{57}Co-cyanocobalamin. Despite this, and he need t measure protein binding this method is less laborious than the measurement of inulin learance It ca be combined th the simultaneous determination of effective renal plasma flow using ^{131}I-labeled Hippuran as Cutler and Glatte howed For routine laboratories, the introduction of these

isotope tech iques greatly simplify the measure ment of enal clear nces

T H Fol y B Sc M B M R C P
N F Jones M A M D M R C P
H F Cl pham B Sc
Department of Med ne
St Thomas H pital Medical School
nd Radioisotope Laborator
St Thomas H pital
London S E 1 Engl nd

REFERENCES

1. Sm th H W The kidney New York 1951 Oxford U vers ty Press
2. Thomas, S Solut excretion man dur ng changing urine flow oc urring pontaneously and induced b sopress jection, J Cl Invest 43 1 1964
3. M ller B F Leaf A Mamt A R and Miller Z N lid t of endogenous creati ine learance as measure of glomerular filt tion te the diseased h ma kidney J Cl n I vest 31:309 1952
4. Berl ne G M Nil arangkur S Varley H and H ner s, M Endogenous cre tinine lear ce and glomerula filt tion rat Lancet 2:874 1964
5. Nelp, W B Wagner H N and Reba, R C. Renal excret on of itam B and ts use in the measurement of glomerular filtration rate in man, J Lab & Cl Med 63:480 1964
6. Cutler R E and Glatte, H Simultaneous measureme t of glomer lar filtr tion te and effect enal pla ma flow th [57]Co-cy noco-balamin nd [131]I H ppur J Lab & Clin Med 65 1041 1965
7. Breckenridge, A nd Metcalfe-Gibson, A. Method of me suring glomerular filtration ate comparison of ull vitami B and creatinine clearances, Lancet 2 65 1965.
8. Malamos, B Dontas, A. S. Koutras, D A., Marketos, S. Sfontouris, J nd I panicolaou N The determination of glomerular filtration rate in cli ical practice, Lancet 1:943 1966.
9. Foley T H Jones, N F and Clapham, W F R nal lear nce of [57]Co-cyanocobalamin Importance of plasma-protei binding, Lancet 2:86, 1966
10. Miller O N Determination of bound vit mi B Arch. Biochem Biophys. 68:255 1957
11. Ekins, R P Nashat F S Portal, R. W and Sgher l, A. M Determination of glomerular filtration rate Lancet 2 109 1966
12. Gregory H F and Holdsworth L. S. A tudy of protein bind ng the metabolism of vitam B Biochem J 73:549 1959
13. Gottlieb C Lau, K. S Wasserman, I R., and Herbert V Rapid harcoal assay for I trinsic factor (IF) ga tric j ice unsaturated B binding capacity t body to IF nd serum nsatur ted B_{12} binding capacity Blood 25:875, 1965
14. Slapak, M and Hume D M A new method of estim ting glomerular filtration rat Use of diminishing blood concentration of labelled vitamin B_{12} Lancet I 1095 1965
15. Aurell, M Estimating glomerular filtration t Lancet 2 188 1965
16. Ekins, R P Nashat, F S nd Portal R. W Measuring glomerular filtr tion rate Lancet 1:364 1966.
17. De Vries, L. A., and Goudsmit, R Measuring glomerular filtration ate Lancet 1:395 1966.

The nature of the increased vascular resistance in chronic hypertension

There is much evidence that although the blood pressure may be raised by riety of mecha isms (renal endocrine nerv us) hypertension in it fully dev loped state is maintained by mechanism different from that hich in tiated it nd that the various etiological types of hypertension end in a final common pathway.[1-3] Recently there has been considerable support for the suggestion that this common path y is due t the development of medial hypertrophy in the small muscula arteries.

Hemod namic studies in patients ith chronic hypertension have shown that there is usually increase in peripheral vascular resistance that this increased resistance is distributed more or less uniformly throughout the body nd that it is situated in the small muscular arteries. It is suggested that this accords well with the distribution of medi l hypertrophy

It may seem surprising t question the existence of medial hypertrophy in the small muscul ar teries but it i necessary to do so. What in fact is the evidence? The increased all t lumen tio in these vessel ? This is not proof of medial hyp trophy it might equally ll be due to rterial constriction.

The only way t scertain hether there is increase in the amount of tissue in the vessel all is to measure it cross-sectional area. Only in the last few years has this been done in any y tematic

ay and in so fa as the systemic circulation is concerned, the measurements have been limited to the superior mesenteric artery and its branches. The results are interesting and perhaps unexpected I the 6 largest branches of the superior mesenteric artery the cross-sectional area of the walls was approximately twice the normal[8] but in the mesenteric and arteriolar branches there was no increase in cross-sectional area, and in arteries of certain sizes there was even a decrease

If the superior mesenteric arterial territory is representative of the systemic circulation generally in chronic hypertension, it ppears that there is no medial hypertrophy in the arterioles (the vessels in hich the main increase in vascular resistance is believed to reside) so that the increased wall to lumen ratio in these vessels must be due to contraction.

This leads to farther question. What is the nature of the arteriolar contraction? I it rapidly reversible vasoconstriction condition of hypertonus, or is it a more permanent contraction I some of these studies, the arteries were distended as fully as possible by injecting a warm suspension of bismuth oxychloride (or barium sulf te) and gelatin into the superior mesenteric artery t pressure of 150 t 250 mm Hg I the cases in which there had been hypertension during life, the injection as made t higher pressure than in the controls the pressure of injection roughly corresponded to the systolic pressure during life. After the injection, the rteries and arterioles in the intestinal wall all appeared to be f lly distended, as judged by the fact that the internal elastic lamina was everywhere quite smooth However when these distended arterioles from the hypertensiv cases ere compared th the corresponding arterioles from control cases, it found that their caliber as significantly educed—in spite of the fact that they had been injected t higher pressure. The reduction in caliber was found to be greatest over the range of 70 to 200μ. (The corresponding diameter in routine microscopic preparations, where the arteries are collapsed, would be approximatel 45 t 120μ.)

Thus, the increased wall to lumen ratio of th arterioles in chronic hypertension is due not t hypertrophy but to contraction These vessels, although still capable of wide ariation i caliber are unable to dilate as f lly as in the normal case It is postulated that in the early stages of hypertension the arterioles are in state of reversible "hypertonus, but that, as the hypertension enter the chronic phase, a persistent shortening of some of the elements of the arteriolar wall takes place, leading to an intrinsic increase in peripheral vascular resistance. Hypertrophy develops in the larger arteries proximal to the zone of contraction.

David Short M.D
Royal Infirmary
Aberdeen Scotland

REFERENCES

1. Pickering G. High blood pressur London 1955 J & A. Churchill, Ltd
2. Wilson, C Control of vascular tone in h per ten ion, Harrington, M editor H pot nsive drugs, London 1956 Pergamon Press.
3. Folkow B Structural, m ogenic h moral nd nervous factor controlling peripheral resistance, Harington.
4. Pickering G. The nature of essential hyper tension, London, 1961 J & A Churchill, Ltd
5. Freis, E. D Haemod namic of h pertension, Phy iol. Rev 40:27 1960
6. Barrett, A M Arterial measurements in the interpretation of cardiomegaly t necropsy cardiac hypertroph and myocardial infarction, J P th Bact 86:9 1963
7. Short, D S Morphology of the intestinal arterioles in chronic h m k pertension, Brit. Heart J 28 184 1966.
8. Short D S The ascular fault in chronic h pertension Lancet 1 1302 1966

Antibiotic persistence during renal failure and dialysis

Toxicity from drugs retained cumulativ ly during renal insufficienc y an be prevented if the possibility is considered be dosage schedules are selected At the same time further modification of dosage sched le ma be necessary if concentrations are be kept hin her peutic ranges hen hemodialys s t ea ment is interposed I formation upon hich t base these adj stment in dosage is seriously meager except for considerable amou of area ingf l study which has been oncluded on tibiotics

Vancomycin, kanam cin neomy in streptomycin, and olistin are currently used antibiotics that are now know to depend primarily upon glomerular filtra ion for clearance from the serum thereby requiring reduction in dosage during renal ficiency if cumulativ toxici y is to be void

estingly ototoxicity is a possible injury common to each, and for reasons unclear

Concerning vancomycin its chief toxic manifestation deafness has been reported[1,2] association with moderate concentrations in the blood, almost exclusively in patients with impaired renal function. The effects of severe renal failure and of hemodialysis on serum concentrations of vancomycin were reported recently by Lindholm and Murray. Surprisingly after 1-Gm doses given intravenously to patient with oliguric chronic renal failure an average of 21 days elapsed before the serum concentrations fell below the minimal inhibitory concentrations for *Staphylococcus aureus* compared to only 1 day in the case of normal individuals. Hemodialysis did not noticeably alter this severely impaired rate of disappearance from the serum and studies in special batch dialyzer employing the same cellophane used in the hemodialyzer gave further evidence that it is so slowly dialyzed that the dosage need not be modified because of periodic hemodialysis treatment. However the report by Boen[4] that it diffuses easily through the peritoneal membrane suggests that removal during peritoneal dialysis may be significant and needs further investigation.

On the basis of these studies dosage schedule of 1 Gm of vancomycin intravenously every 10 to 14 days recommended for the treatment of staphylococcal infections in oliguric adult patients, regardless of hemodialysis treatment. The resulting serum levels ranging between 5 and 20 mg per milliliter are considered to be therapeutic and safe. Our further observation has been that the clinical response has been appropriate for such levels and not dependent on the total dose. In other words, fortuitous blessing of the impaired excretion of vancomycin in patients with renal failure is that single dose may last the full therapeutic course.

Regarding kanamycin Kunin reported finding rather high levels still in the serum of anuric patients 4 to 5 days after single 1-Gm intramuscular doses. Its ... readily dialysis from serum across a cellophane membrane has been reported and some decrease in serum levels by hemodialysis has been claimed. In fact Maher and Schreiner[6] reported that with the twin-coil Kolff dialyzer the levels are reduced by about 50 per cent of the control concentration in 8 hours giving us a rough guide to the adjustment of dosage during hemodialysis. Removal by peritoneal dialysis has not yet been quantitated.

Neomycin closely resembles kanamycin chemically and pharmacologically and in the way it accumulates in the blood of patients with impaired renal function according to Kunin and associates. Information concerning its dialyzability through either cellophane or peritoneal membrane is still wanting but could expectedly be similar to that of kanamycin.

Streptomycin was found to have half life of 2 to 5 days in the serum of anuric patient and in one case the drug was still detectable 20 days after the last dose. Dialyzability of it has been demonstrated in vitro as well as appreciable decreases in blood levels during hemodialysis according to Edwards and Whyte. Significantly arteriovenous difference of 4 per cent has been measured across the artificial kidney suggesting that the dosage schedule should be liberalized during times of hemodialysis, but how much remains uncertain. Removal during peritoneal dialysis has not been defined

Serum levels of colistin were not affected by hemodialysis for 5 to 5½ hours using the Kolff twin-coil artificial kidney in studies by MacKay and Kaye.[10] Peritoneal dialysis may have decreased the serum levels in one case studied but probably not significantly. They concluded that anuric patients given one injection of 2.0 mg per kilogram may be expected to maintain therapeutic levels for many days, probably until diuresis occurs, even if undergoing dialysis treatment.

The demand is increasing for information upon which to base drug dosages for patients with renal insufficiency and patients undergoing dialysis. It is hoped that such information can be provided in form sufficiently simple and clear cut that the clinician can guide therapy predictably and without having to depend routinely upon the availability of laboratory analysis of samples of body fluid. Information inherent would also define the relative value of dialysis in the treatment of drug overdosages.

Dale D Lindholm M.D
Department of Medicine
Tulane University School of Medicine
New Orleans La 70112

REFERENCES

1. Leach, W. Ototoxicity of neomycin and other antibiotics, J Laryng & Otol. 76 774 1962.
2. Geraci, J. E. Heilman, F. R., Nichols, D. R., and Wellman, W. E. Antibiotic therapy of bacterial endocarditis. VII Vancomycin for acute micrococcal endocarditis. Preliminary report, Proc. Staff Meet Mayo Clin. 33 172, 1958.
3. Lindholm, D. D. and Murray J. S.: Persistence of vancomycin in the blood during renal failure and its treatment by hemodialysis, New England J Med. 274 1047 1966.
4. Kunin, C. M. and Finland, M.: Persistence of antibiotics in blood of patients with acute renal failure. III. Penicillin, streptomycin, erythromycin and kanamycin, J Clin. Invest. 38 1509 1959
5. Doyle J. E. Extracorporeal hemodialysis therapy in blood chemistry disorders, Springfield, Ill. 1962, Charles C Thomas
6. Maher J. F. and Schreiner G. E. The clinical dialysis of poisons, T. Am. Soc. Artificial Int. Organs 11:349 1965.
7. Kunin, C. M. Chalmers, T. C., Leevy C. M. Sebastyan, S. C., Lieber C. S. and Finland, M.: Absorption of orally administered neomycin and kanamycin, with special reference to patients with severe hepatic and renal disease. New England J Med. 262:380, 1960
8. Edwards, K. D. G. and Whyte, H. M. Streptomycin poisoning in renal failure. An indication for treatment with an artificial kidney Brit. M. J. 1 753, 1959
9. Kunin, C. M. and Finland, M. Restrictions imposed on antibiotic therapy by renal failure Arch. Int. Med. 104 1030, 1959
10. MacKay D. N. and Kaye D.: Serum concentration of colistin in patients with normal and impaired renal function, New England J. Med. 270:394 1964.

Cardiogenic shock treated with infusion of dextrose solution

The term *shock* in acut myocardial infarction is used here to define syndrome of pallor hypotension, restlessness and disturbance of consciousness, intense peripheral constriction and nuria, with or without elevation of the central venous pressure. Metabolic acidosis is an in ariable concomitant. Death is likely to follow upon the appearance of the signs, unless they arise from a syncopal reaction that can be treated by altering the posture or a dysrhythmia that can be corrected. The incidence of shock in *cardiac infarction* is said to be 15 per cent, and the mortality 88 per cent. The true mortality is probably nearer to 100 per cent, be cause uthors may have included cases of yncope or of hypotension secondary to dysrhythmia.

It is worth hile t treat the hypotension because it predisposes to metabolic acidosis, dangerous dysrhythmia, nd renal failure, reduces the col lateral blood flow to the ischemic area, reduces the contractility of the myocardium supplied by nar rowed coronary essels, and increases the systolic ballooning of the infarcted area. Therapeutic optimism is encouraged by the observation that the syndrome is more common in the case of occlusion of the branches of a coronary artery than in obstruction of the main stem, and by the urprisingly rapid nd complete recovery of successfully treated patients

The treatment has been pproached in various ways, by transfusion, by asoconstrictive drugs, nd by inotropic agents. Transfusion passed out of favor when measurements of blood volume failed to show deficits, nd vasoconstriction was said to be beneficial even though intense vasoconstriction is the most striking physical sign. In our hands, the vasoconstrictive drugs have neither saved patients in an advanced tage of the syndrome nor halted the progression of the metabolic acidosis that indicates the failure of the circulation If w ever encounter cases of the syndrome i hich the heart function is adequate and in hich asodilatation is responsible for the hypotension we shall be pre pared t consider the use of asoconstrictors!

Vasoconstricti drugs with a inotropic action have yet to prov their value in cardiogenic shock. Their greatest effect may be in the patients ho are syncopal from the sedative drugs that encourage the pooling of blood in those ho are aised head up. Often it is difficult to ean patients off these drugs, nd infusion is required before their administration can be stopped. The thors experience suggest that infusion alone may be adequat treatment.

I our series of cases ith advanced signs nd elevated central venous pressure, the patients were nursed supine and gi en oxygen to brea he Five per cent dextrose solution as given intravenously by drip in doses of 50 t 200 ml t ime The rate of infusion was controlled by obser tion of the central enous pressure the arterial pressure the flow of urine nd the clinical ppearance of the peripheral irculation It as not difficult to resuscitat each patient by using the lowest rat of infusion that improved the arterial pressure and the peripheral circulation nd restored the flow of urine. Pulmonary edema created neither clinical nor therapeutic problem although transitory early signs may have ppeared on the radiographs.

Each dose of the sol tion raised the arterial pressure and lso the venous pressure. The latter as allowed to subside toward its original level before the next dose was given The technique is reminiscent of the treatment of hypotension t the end of heart and lung bypass operations, herein blood is injected f om the machine u til satisfactory level of arterial pressure is achieved. The venous pressure obtained t this point is maintained by intravenous infusion If the i jection from the machine fails to improve the arterial pressure, the enous pressure rises uselessly and the procedure is abandoned.

After the resuscitation the uthors found t necessary to continue the infusion for arying periods before the tendency to hypotension disppeared and left stable circulation I the first case total of 4 1 liters of solution was given in 20 hours in the second 2.1 liters in 12 hour nd in the third 12.3 liters in 1 eek.

A fourth case, not previously described, is illustrativ A 76-yea -old man collapsed suddenly and was brought to hospital 2 hours later t 7 P.M He as extremely ill and pale the circulation in the arm, fingers, and toes as greatl reduced the systolic blood pressure was between 90 and 100 mm Hg the mental cond tion aried bet een st por nd semiconscious restlessness, nd the rapidity of his deterioration was obvious. H had been t ork earlier in the day and preparing for his marriage and it as decided to treat him igorously During his transfer t he in ensi e-care unit the heart rate slowed to 40 per minute, the trunk became mottled ith cy notic patches of stasis, and the fingers nd ear ere blue His supine position mainta ned nd the legs ere elev ted oxygen as given by face-mask, and tropine sulphate, 0.5 mg as injected intra enousl His deterioration continued A ardiac heter as introduced at the superior ena ca a from an arm ein an indwelling needle as inserted int the brachial artery and he bladder as catheterized

Analysis of arterial blood showed pH, 7.35 oxygen saturation 97 per cent, and metabolic acidosis of −6.5 mEq./L., as determined by the Siggard-Anderson nomogram The acidosis was corrected with an intravenous infusion of 8.4 per cent sodium bicarbonate solution. The arterial pressure recorded ith an electromanometer 55 15 mm Hg and the cen ral enous pressure (CVP) 7 cm of w ter above the zero level set the sternal ngle (8 15 M., Fig. 1) N urine as formed. The electrocardiogram (ECG) showed slow trial fibrillation ith ectopic beats, and marked current of injury

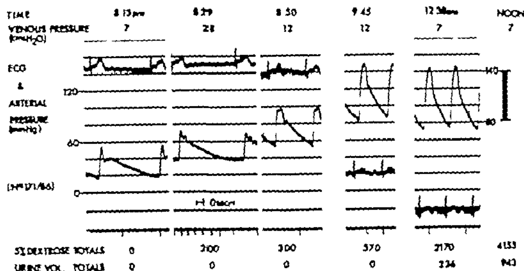


Fig. 1 The arterial pressure and the electrocardiogram during treatment with infusion of dextrose. At corresponding times the total amount of dextrose given and the urine secreted are shown together with the central venous pressure.

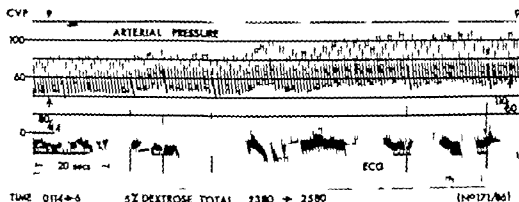


Fig. 2 A continuous recording of the arterial pressure and electrocardiogram from 1.14 to 1.16 A.M. during the infusion of 200 ml. of dextrose. There was no detectable difference between the venous pressure at the beginning and that at the end of the infusion.

At 8.13 P.M. the infusion of 5 per cent dextrose solution into the inferior vena cava was begun and the first 200 ml. was given in 10 minutes. This raised the CVP to 28 cm of water but also raised the arterial pressure to 70/40 mm.Hg (8.29 P.M. Fig. 1). Within 16 minutes, the CVP fell to 12 cm of water and further doses of 100 to 200 ml. of 5 per cent dextrose were given. The arterial pressure reached a peak of 150/80 mm Hg (9.45 P.M. Fig. 1), the heart rate increased, and the changes in the shape of the arterial pressure pulse were consistent with a marked increase in the stroke volume.

Each successive dose of the dextrose solution raised the venous pressure by a smaller amount and for a shorter period until, at 1.14 A.M., 5 hours after the treatment began, 200 ml. was absorbed in 2 minutes without affecting the CVP. The arterial pressure rose from 80/44 to 110/60 mm.Hg (Fig. 2).

The raising of the arterial pressure with the treatment was accompanied by other signs of improvement. The first was recovery of mental clarity and calmness after a half hour of infusion. After 2 hours the urine flowed and the ECG current of injury diminished. After 4 hours the peripheral circulation seemed to be normal, and the atrial fibrillation reverted to sinus rhythm (12.38 A.M. Fig. 1).

By noon on the day after admission he looked well, and took an alert interest in his surroundings. The blood pressure was stable at 140/80 mm.Hg without infusion, and the CVP was 7 cm. of water. The infusion was stopped. A total of 4.155 having been given in 16 hours, during which 913 ml of urine was passed.

Four days later he was active in bed, the blood pressure was 160/85 mm.Hg and the CVP 2 cm of water. Now he has returned to normal activity and is free from heart failure.

It may be considered that this patient and the

others, recovered spontaneously despite the massive infusion but it is our belief that he was soon to die and that the infusion resuscitated him.

Another patient was similarly resuscitated but died suddenly during convalescence. Two others failed to respond to the infusion, and neither norepinephrine nor epinephrine had any clinically detectable effect upon the circulation. Autopsy revealed severe myocardial damage from previous infarctions.

It has been suggested that the presence of congestive heart failure in cardiogenic shock indicates "limited reserve of the circulatory system and that intravenous infusion may be injudicious and dangerous, overfilating the heart further reducing the cardiac output and aggravating the shock." In the patient described here the central venous pressure was abnormally high (7 cm. H_2O) at the start of the treatment and yet the restoration of the blood pressure, peripheral circulation, and flow of urine, and his recovery suggest that the infusion was beneficial. This raises the question of whether the elevation of the venous pressure really was a sign of congestive heart failure or whether it indicated some other phenomenon. We suggest that it was a sign of constriction of the venous system the evidence being the great increase in the venous pressure from 7 to 28 cm. H_2O when 200 ml. of 5 per cent dextrose first was added to the circulating blood volume. This contrasts with the response at a later stage after the circulation had improved with the infusion of 2,380 ml. of 5 per cent dextrose when a dose of 200 ml. was absorbed without altering the central venous pressure, presumably because the venous constriction had disappeared.

The explanation of the beneficial effect of infusion may lie in the experimental observations of Ross[9] He has shown that the recently injured ventricle requires distention before its output can be restored to maintain the pre-injury level of arterial pressure. We suggest that infusion resuscitated our patients by distending the heart to the point at which its output was adequate for the maintenance of life. Clinically there are many similarities between hemorrhagic and cardiogenic shock. In the former the important disturbance is a deficiency of the effective blood volume. In our cases of recoverable cardiogenic shock the important disturbance may have been a sudden deficiency of the normal blood volume in relation to the needs of the newly injured heart.

Ectopic activity was abolished or minimized under treatment with infusion. One reason for this may have been an improvement in the coronary circulation consequent upon the volume-expanding effect of the infused solution. Another reason may have been the potassium-shifting or biochemical effect of the infused dextrose.[10]

We attempted our infusion treatment in desperate clinical situations in which death seemed to be imminent and in which the alternative methods had proved valueless on previous occasions. We recognize that infusion may be extremely hazardous in acute cardiac infarction and consider that it should be attempted only when there is adequate standard of intensive care and when the complication of pulmonary edema, if it should occur, can be treated with intermittent positive pressure ventilation.

Our experience suggests that some of the patients who appear to be dying from cardiogenic shock are recoverable with infusion whereas others have irreparably damaged hearts. Neither the sizes nor the distinguishing signs of the groups are known at present. Tentatively it is suggested that a solution of 1 ml. of 1/1,000 epinephrine hydrochloride in a 500-ml. unit of 5 per cent dextrose may be dripped slowly intravenously in patients in whom one or two doses of dextrose solution have proved to be ineffective. The patient in shock who responds neither to the volume-expanding and biochemical effects of the dextrose nor to the powerful inotropic effect of the epinephrine probably has too little viable myocardium to survive without an artificial circulation.

P. G. F. Nixon, M.R.C.P.
H. Ikram, M.R.C.P.
S. Morton, S.R.N.
Cardiac Department and
Intensive-Care Ward
Charing Cross Hospital
London, W.C.2, England

REFERENCES

1. Epstein, F. H., and Relman, A. S.: Transfusion treatment of shock due to myocardial infarction, New England J. Med. 241:2889, 1949.
2. Estes, E. H. J., Entman, M. L., Dixon, H. B. II, and Hackel, D. B.: The vascular supply of the left ventricular wall. Anatomic observations, plus a hypothesis regarding acute events in coronary artery disease, Am. Heart J. 71:58, 1966.
3. Hellerstein, H. K., Brofman, B. L., and Caskey, W. H.: Shock accompanying myocardial infarction. Treatment with pressor amines, Am. Heart J. 44:407, 1952.
4. Corday, E., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Spritzler, Ramon J., and Prinzmetal, M.: Studies on the coronary circulation IV. The effect of shock on the heart and its treatment, Am. Heart J. 37:560, 1949.
5. Kurland, G. S., Weingarten, C., and Pitt, B.: The relation between the location of coronary occlusions and the occurrence of shock in acute myocardial infarction, Circulation 31:646, 1965.
6. Nixon, P. G. F., Ikram, H., and Morton, S.: Infusion of dextrose solution in cardiogenic shock, Lancet 1:1077, 1966.
7. Botticelli, J. T., Tsagaris, T. J., and Lange, R. L.: Mechanisms of pressor amine dependence, Am. J. Cardiol. 16:847, 1965.
8. Berman, E. F., and Akman, L. C.: Intra-arterial infusion in the treatment of shock resulting from coronary occlusion, Am. Heart J. 43:264, 1952.
9. Ross, J. J.: Personal communication, 1966.
10. Sodi-Pallares, D.: Possibility of a therapy of cellular ion integration in cardiovascular diseases, Arch. Inst. Card. de Mexico 31:537, 1961.
11. Mittra, B.: Potassium, glucose and insulin in treatment of myocardial infarction, Lancet 2:607, 1965.

Announcements

INTERNATIONAL SYMPOSIUM An International Symposium on the *Pharmacology of Hormonal Polypeptides Metabolic and Molecular Aspects* will be held i Milan It ly September 14-16 1967 under the o-sponsorship of the U ersity of Milan Instit tut of Pharmacology nd Therapy Italy and the Stat Univer ty of New York at *Buffalo* Depart me t of Bioch mical Pharmacology School of Pharmacy Buff lo, New York. The Symposium is under the uspices of the I ternational Society for Biochemical Pharmacology

Th S mposium h been d ided into the follow ing sessions Techniques in Peptide Synthesis An terior P tu tary nd Placental Hormones Ant rior P t tary and H pothalamic Hormones Posterior P t tary Hormones nd Factors Affecting Lipid Mob lizatic I sul nd Glucagon Othe Hor *monal Peptides*

Deadline f r ad nced registration and hotel reserv tion is J ne 30 1967

F r informatio nd forms please contact Professor N Back Chairma Department of Biochem l Pharmac logy School of Pharmacy State U t f N w York t Buffalo Buffalo New York or F of I Martin and R Paoletti Institut of Pharma logy University of M lan Via Andrea Del Sarto 21 M la It ly

MEDICAL RESEARCH GRANTS AND FELLOWSHIPS The Lif Insurance Medical Research Fund ha announced *Sept 15 1967* as the deadline for receipt of applications for Grants in Aid of medical research, to become effective July 1 1968. These grants re made t non-profit institutions for support of basic research in physiology biochemistry nd other fields related to medicine. Further information and application forms may be obtained by interested in estigators from the Scientific Director Lif Insurance Medical Research Fund 1030 East Lancaster A e nue Rosemont, Pennsylvania 19010

The Fund also offers Medical Scientist Fellowships t medical students willing to prepare for careers in teaching nd research by securing both the M D and the Ph D or its equivalent. The Fellowships offer maximum of six years of aid F llowships can be activated at arious stages of the M D Ph D training Each school of medicine is invited to make tw *nominations for aid to begin* July 1 1968. Deadline for receipt of pplications from deans offices is *Oct 15 1967* Further information can be obtained from deans in schools of medicine

The Rogers Heart Foundation is sponsoring WORKSHOP IN ELECTROCARDIOGRAPHY at the Tides Bath Club Redington Beach Fla. from June 26 through J ne 30 1967 Henry J L. Marriott M D is the director *For further details write the Rogers* Heart Foundation 500 First Federal Building St. Petersburg Fla.

Author index*

*January, pp. 1-144; February, pp. 145-292; March, pp. 293-430; April, pp. 431-578; May, pp. 579-722; June, pp. 723-864.

T

V

W

Y

Z

Subject index*

*January pp 1 146 February pp 147 292 March pp 293-438 April pp 439 578 May pp 579 722 June pp 723-864

B

C

I

R

S

T

U